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FEE TRANSMITTAL for FY 2004 <small>Effective 10/01/2003, Patent fees are subject to annual revision.</small>		Complete if Known	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27		Application Number	Patent#: 5843901
TOTAL AMOUNT OF PAYMENT (\$) 200.00		Filing Date	Issued: December 1, 1998
		First Named Inventor	Roger W. Roeske
		Examiner Name	Not Yet Assigned
		Art Unit	N/A
		Attorney Docket No.	PPI-007

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 12-0080

Deposit Account Name: Lahive & Cockfield, LLP

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity	Small Entity	Fee Description	Fee Paid
Code (\$)	Code (\$)		
1001 770	2001 385	Utility filing fee	
1002 340	2002 170	Design filing fee	
1003 530	2003 265	Plant filing fee	
1004 770	2004 385	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	
SUBTOTAL (1) (\$)			0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims: -20** = x =

Independent Claims: -3** = x =

Multiple Dependent: =

Large Entity	Small Entity	Fee Description	Fee Paid
Code (\$)	Code (\$)		
1202 18	2202 9	Claims in excess of 20	
1201 86	2201 43	Independent claims in excess of 3	
1203 290	2203 145	Multiple dependent claim, if not paid	
1204 86	2204 43	** Reissue independent claims over original patent	
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent	
SUBTOTAL (2) (\$)			0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity	Small Entity	Fee Description	Fee Paid
Code (\$)	Code (\$)		
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for <i>ex parte</i> reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 420	2252 210	Extension for reply within second month	
1253 950	2253 475	Extension for reply within third month	
1254 1,480	2254 740	Extension for reply within fourth month	
1255 2,010	2255 1,005	Extension for reply within fifth month	
1401 330	2401 165	Notice of Appeal	
1402 330	2402 165	Filing a brief in support of an appeal	
1403 290	2403 145	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,330	2453 665	Petition to revive - unintentional	
1501 1,330	2501 665	Utility issue fee (or reissue)	
1502 480	2502 240	Design issue fee	
1503 640	2503 320	Plant issue fee	
1460 130	1460 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1806 180	1806 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 770	2809 385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 770	2810 385	For each additional invention to be examined (37CFR 1.129(b))	
1801 770	2801 385	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	
Other fee (specify)		1455 Filing an application for patent term adjustment	200.00
*Reduced by Basic Filing Fee Paid			SUBTOTAL (3) (\$) 200.00

SUBMITTED BY (Complete if applicable)

Name (Print/Type)	Jane E. Remillard	Registration No. (Attorney/Agent)	38,872	Telephone	(617) 227-7400
Signature	<i>Jane Remillard</i>	Date	January 9, 2004		

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EL 982 739 183 US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: January 9, 2004 Signature: *Jane Remillard* (Jane E. Remillard)

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#31

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No. 5,843,901
Issued: December 1, 1998
Name of Patentee: Roger W. Roeske

Title: LHRH Antagonist Peptides

Attorney Docket No.: PPI-007

MailStop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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"Express Mail" mailing label number EL 982 739 183 US

Date of Deposit January 9, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to MailStop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Signature

Jane E. Remillard, Esq.

Please Print Name of Person Signing

APPLICATION FOR PATENT TERM EXTENSION PURSUANT TO
35 U.S.C. §156 AND 37 C.F.R. §1.740

Dear Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.740, PRAECIS PHARMACEUTICALS INCORPORATED ("PRAECIS") hereby applies for extension of the term of U.S. Patent No. 5,843,901, issued December 1, 1998. PRAECIS represents that it is the Marketing Applicant and agent acting on behalf of The Advanced Research and Technology Institute, the assignee of the entire interest in U.S. Patent No. 5,843,901 by virtue of an assignment from the Indiana University Foundation dated June 30, 1997, a copy of which is submitted herewith as Exhibit. The Indiana University Foundation had in turn acquired ownership of the patent via an

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01 FC:1457 1120.00 DA

assignment from the inventor dated August 25, 1995 and recorded in the United States Patent and Trademark Office on November 6, 1995 at reel 7706, frame 0614.

A Power of Attorney dated December 29, 2003 from The Advanced Research and Technology Institute, authorizing the registered practitioners of Lahive & Cockfield, LLP to act on behalf of the assignee, with correspondence and communications to be directed as set forth therein, is submitted herewith as Exhibit H. Accordingly, as required under 37 CFR § 3.73(b)(2)(i), the undersigned is authorized to act on behalf of The Advanced Research and Technology Institute in submitting this Application.

A Power of Attorney dated December 23, 2003 from PRAECIS authorizing the registered practitioners of Lahive & Cockfield, LLP to act on behalf of Applicant, with correspondence and communications to be directed as set forth therein, is submitted herewith as Exhibit I.

Applicant also represents that it was formerly named Pharmaceutical Peptides Inc., having changed its name to PRAECIS PHARMACEUTICALS, INC. on November 22, 1996, and having further changed its name from PRAECIS PHARMACEUTICALS, INC. to PRAECIS PHARMACEUTICALS INCORPORATED on June 9, 1997.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §§1.710-1.775.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is Plenaxis™ containing as active ingredient abarelix (PPI-149), a decapeptide analogue of the naturally occurring luteinizing hormone releasing hormone (LHRH). Abarelix is an LHRH antagonist, which is further identified as follows;

Formula:

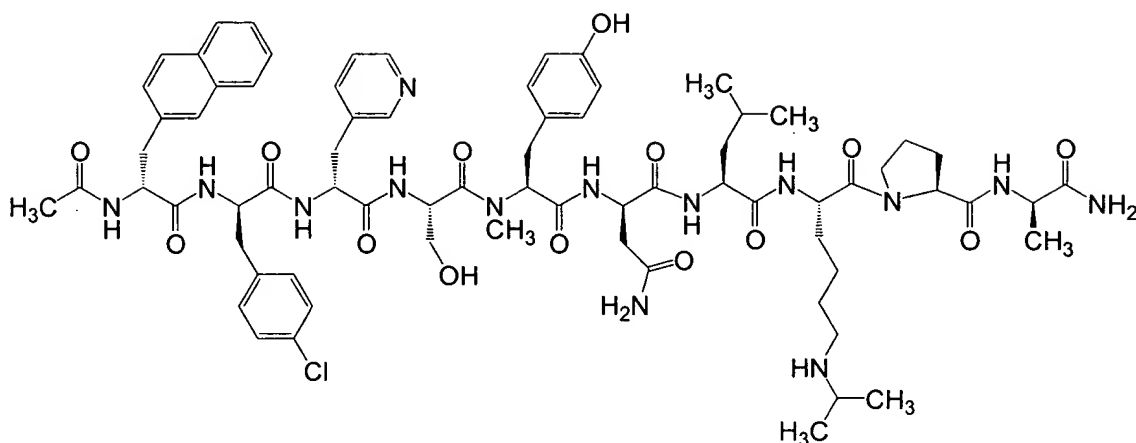
Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-MeTyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-NH₂.

Chemical name:

acetyl-D-β-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyl-tyrosyl-D-asparagyl-L-leucyl-L-N(ε)-isopropyl-lysyl-L-prolyl-D-alanyl-amide

Structural formula:





Molecular formula (free base): C₇₂H₉₅O₁₄N₁₄Cl

Molecular weight (free base): 1416.06 g/mole

CAS Registry Number: 183552-38-7

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The Regulatory review for the above-identified product occurred under Section 505 of the Federal Drug, Food and Cosmetic Act (21 U.S.C. §355).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Plenaxis™ received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b)) pursuant to the approval of NDA 21-320 on November 25, 2003.

(4) In the case of a drug product, an identification of each active ingredient in the product and, as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in

combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of Plenaxis™ is abarelix, which has not been approved for commercial marketing or use under the Food, Drug and Cosmetic Act prior to the approval of NDA 21-320 on November 25, 2003.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 1.720(f) and an identification of the last day on which the application could be submitted.

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The product was approved on November 25, 2003, and the last day on which this application could be submitted is January 24, 2004.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue and the date of expiration.

An extension is being sought for U.S. Patent No. 5,843,901, which issued on December 1, 1998 in the name of Roger W. Roeske and expires on December 1, 2015.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A complete copy of U.S. Patent No. 5,843,901 is attached hereto as Exhibit A.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of the receipt of maintenance fee payment is attached hereto as Exhibit B. No certificate of correction, disclaimer or reexamination certificate has been filed or issued in U.S. Patent No. 5,843,901.

(9) A Statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:
(i) The approved product, if the listed claims include any claims to the approved product;

- (ii) The method of using the approved product, if the listed claims include any claim to the method of using the claimed product; and
- (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacture of the approved product.

Claims of U.S. Patent No. 5,843,901 read on the approved product and pharmaceutical compositions comprising the approved product.

Claim 3 of this patent is specifically drawn to the approved product as follows:

3. A peptide compound comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-N-Me-Tyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-NH₂;
or a pharmaceutically acceptable salt thereof.

Generic product claim 1 is as follows:

1. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal;

B is His or 4-Cl-D-Phe;

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;

D is Ser;

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala,
Arg or Ile;

F is D-Asn or D-Gln;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂ ;

or a pharmaceutically acceptable salt thereof.

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This claim reads on the approved product when A is Ac-D-Nal; B is 4-Cl-D-Phe; C is D-Pal; E is N-Me-Tyr; F is D-Asn; G is Leu; H is Lys(iPr); and J is D-Ala-NH₂.

Generic product claim 2 is as follows:

2. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal;

B is His or 4-Cl-D-Phe;

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;

D is Ser;

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is D-Asn;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂ ;

or a pharmaceutically acceptable salt thereof.

This claim reads on the approved product when A is Ac-D-Nal; B is 4-Cl-D-Phe; C is D-Pal; E is N-Me-Tyr; G is Leu; H is Lys(iPr); and J is D-Ala-NH₂.

Claim 5 of this patent reads on a pharmaceutical composition comprising the approved product as it depends on Claims 1, 2 or 3:

5. A pharmaceutical composition comprising the peptide of any one of claims 1, 2, 3 or 4, and a pharmaceutically acceptable carrier.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

- (i) For a patent claiming a human drug, antibiotic, or human biological product:**
(A) The effective date of the investigational new drug (IND) application and the IND number;

The IND application for Plenaxis™ was submitted on October 18, 1996, and the IND became effective on November 17, 1996. By letter dated October 22, 1996, the FDA acknowledged receipt of the IND application on October 18, 1996, and assigned IND number 51,710. A copy of this letter attached as Exhibit C¹. This establishes the beginning of the “regulatory review period” under 35 U.S.C. §156(g) as November 17, 1996.

- (B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and**

NDA Number 21-320 for Plenaxis™ was submitted on December 11, 2000. The FDA confirmed the receipt of the NDA on December 12, 2001 in a letter dated January 8, 2001, a copy of which is attached hereto as Exhibit D. This establishes December 11, 2000 as the initial submission date of the NDA for the approved product for the purposes of 35 U.S.C. § 156(g)(1). On June 11, 2001, PRAECIS received a Non-Approvable Letter from FDA for NDA 21-320. PRAECIS resubmitted NDA 21-320 in NDA Amendment 042 on February 25, 2003, as a complete response to the June 11, 2001 Non-Approvable Letter. By letter dated March 18, 2003, FDA acknowledged receipt of the February 25, 2003 resubmission to NDA 21-320. A copy of this letter is attached as Exhibit E.

- (C) The date on which the NDA was approved or the Product License issued.**

¹ Applicant also represents that it was formerly named Pharmaceutical Peptides Inc., having changed its name to PRAECIS PHARMACEUTICALS, INC. on November 22, 1996, and having further changed its name from PRAECIS PHARMACEUTICALS, INC. to PRAECIS PHARMACEUTICALS INCORPORATED on June 9, 1997

The NDA was approved by the FDA approval letter sent November 25, 2003, setting the effective date of the approval as the November 25, 2003 date of the letter. A copy of this FDA approval letter is attached as Exhibit F. This establishes the end of the “regulatory review period” under 35 U.S.C. §156(g)(1) as November 25, 2003.

(11) Brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The regulatory activities undertaken to obtain approval of Plenaxis™ commenced with the submission of an Investigational New Drug Application (IND 51,710) on October 18, 1996 to study the use of abarelix acetate/abarelix for injectable suspension for the palliative treatment of advanced prostate cancer.

The testing phase of the regulatory review period consisted of activities occurring under IND 51,710. These activities included meetings with the FDA on June 18, 1997; August 4, 1998; February 10, 1999; April 28, 1999; May 5, 1999; June 18, 1999; and July 20, 2000; and timely submission of numerous documents required by regulation including Annual Reports on December 19, 1997; December 21, 1998; November 29, 1999; February 20, 2001; March 29, 2002; and July 18, 2003; Information Amendments, IND Safety Reports (initial and follow-up), New Protocols and Protocol Amendments. In addition, responses to all FDA Information Requests were promptly submitted.

The testing phase ended and the approval phase of the regulatory review period began on December 11, 2000 when, pursuant to Section 505(b)(1) of the Federal Food , Drug and Cosmetic Act, PRAECIS PHARMACEUTICALS INCORPORATED submitted New Drug Application 21-320 to the FDA. A 3-month Safety Update was submitted on March 13, 2001. Many significant regulatory activities occurred during this approval phase, including numerous responses to FDA Information Requests and draft labeling were submitted in a timely manner. PRAECIS received a Non-Approvable Letter from FDA for NDA 21-320 on June 11, 2001.

PRAECIS continued active communication/interaction with FDA on NDA 21-320 including meetings with FDA on September 10, 2001 and July 18, 2002. A complete response to the Non-Approvable Letter was submitted by PRAECIS on February 25, 2003 commencing the second approval phase of the regulatory review period for Plenaxis™. Many significant regulatory activities occurred during this second approval phase, including an additional Safety Update submitted July 26, 2003, numerous responses to FDA Information Requests and revised draft labeling were submitted.

The regulatory review period for Plenaxis™ ended with permission for commercial marketing being granted by FDA on November 25, 2003. All regulatory activities were carried out in a prompt, timely manner in accordance with all applicable statutes and regulations, reflecting the diligent pursuit of FDA approval of NDA 21-320 for Plenaxis™.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined.

In the opinion of the Applicant, U.S. Patent No. 5,843,901 is eligible for an extension because it satisfies all of the requirements for such extension under 35 U.S.C. §156(a):

(1) 35 U.S.C. §156(a)

As set forth in section 8, U.S. Patent No. 5,843,901 claims the approved product and pharmaceutical compositions comprising the approved product.

(2) 35 U.S.C. §156(a)(1)

U.S. Patent No. 5,843,901 was granted December 1, 1998 on an earliest filed patent application filed on June 7, 1995 and is subject to no terminal disclaimers. As the application was pending on June 7, 1995, the term of the issued patent expires on the later of (a) the date which is 20 years from the filing date of the earliest filed application, or June 7, 2015; and (b) the date which is 17 years from the issue date, or December 1, 2015. The patent therefore expires on December 1, 2015, and this application has been filed before the expiration of the patent term.

(3) 35 U.S.C. §156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. §156(a)(3)

This application is submitted by the Marketing Applicant and authorized agent of the owner of record. The Advanced Research and Technology Institute is the owner of record through an assignment from the Indiana Research Foundation, submitted herewith as Exhibit G. The Indiana Research Foundation had in turn acquired ownership of the patent via an assignment from the inventor dated August 25, 1995 and recorded in the United States Patent and Trademark Office on November 6, 1995 at reel 7706, frame 0614.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the November 25, 2003 approval letter from the FDA (Exhibit F), Plenaxis™ was subject to a regulatory review period under Section 505(b) of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of Plenaxis™ after this regulatory review period is the first permitted commercial marketing of Plenaxis™ under provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which the regulatory review period occurred, as confirmed by the absence of any approved NDA for approved product prior to November 25, 2003.

(7) 35 U.S.C. 156(g)(4)

No other patent has been extended for the same regulatory review period for the product Plenaxis™.

The term of U.S. Patent No 5,843,901 should be extended by 725 days, from December 1, 2015 to November 25, 2017. This extension is calculated as set forth below.

The rules for calculating a patent term extension under 35 U.S.C. §156 are set forth in 37 C.F.R. §1.775.

§1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.

(a) If a determination is made pursuant to Sec. 1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent or any earlier date set by terminal disclaimer (Sec. 1.321).

U.S. Patent No. 5,843,901 issued on December 1, 1998 from an earliest-filed U.S. application filed June 7, 1995. Pursuant to 35 U.S.C. §154, this patent is entitled to an original term of the longer of (1) 20 years from the filing date; and (2) 17 years from the issue date. In this case, 17 years from the issue date is the longer term. Therefore, the original expiration date of the patent is December 1, 2015. No terminal disclaimer has been filed in this case.

(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. §156(g)(1)(B), it is the sum of--

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

As set forth below, the regulatory review period for Plenaxis™ can be viewed in two alternate ways, depending upon whether the period between the receipt of the nonapprovable letter and the filing of the amended NDA falls under paragraph (c)(1) or paragraph (c)(2).

(A) The period between the receipt of the nonapprovable letter and the filing of the amended NDA falls under paragraph (c)(1).

The regulatory review period for Plenaxis™ can be viewed as the sum of (1) the period beginning on November 17, 1996, the date of acceptance of the IND by the FDA, and ending on December 11, 2000, the date the NDA for Plenaxis™ was initially submitted, (2) the period beginning December 12, 2000 and ending June 11, 2001, the date of the non-approvable letter from the FDA, (3) the period from June 12, 2001 to February 25, 2003, the date of the resubmission of the amended NDA, and (4) the period from February 26, 2003 to November 25, 2003, the date of the approval letter from the FDA. In this view, the periods from November 17, 1996 to December 11, 2000 and from June 12, 2001 to February 25, 2003 fall under paragraph (c)(1). The periods from December 12, 2000 to June 11, 2001 and from February 26,

2003 to November 25, 2003 fall under paragraph (c)(2). The resulting regulatory review period is 2,565 days.

(B) The period between the receipt of the nonapprovable letter and the filing of the amended NDA falls under paragraph (c)(2).

In this view, the regulatory review period for PlenaxisTM is the sum of (1) the period beginning on November 17, 1996, the date of acceptance of the IND by the FDA, and ending on December 11, 2000, the date the NDA for PlenaxisTM was initially submitted, and (2) the period beginning December 12, 2000 and ending November 25, 2003, the date of the approval letter from the FDA. In this view, the period from November 17, 1996 to December 11, 2000 falls under paragraph (c)(1), and the period from December 11, 2000 and ending November 25, 2003 falls under paragraph (c)(2). The regulatory review period for PlenaxisTM was thus 2,565 days.

(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. §156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;

The number of days in the regulatory review period which were on or before the issue date of the patent is 745. Subtracting 745 days from the regulatory review period leaves 1,820 days. As set forth in Section 10 above, there were no days in the regulatory review period during which the applicant did not act with due diligence.

As set forth above, the number of days remaining in the period defined by paragraph (c)(1) following reduction in accordance with paragraphs (d)(1)(i) and (d)(1)(ii) depends upon

whether the period from June 12, 2001 to February 25, 2003 falls under paragraph (c)(1) or paragraph (c)(2). Calculations for both of these alternatives are set out below.

(A) The period from June 11, 2001 to February 25, 2003 falls under paragraph (c)(1).

The total number of days in the regulatory review period which fall under paragraph (c)(1) is 2,109. Subtracting from this the number of days which were on or before the issue date of the patent leaves 1,364 days. Subtracting one-half of 1,364 from 1,820 leaves 1,138 days.

(B) The period from June 11, 2001 to February 25, 2003 falls under paragraph (c)(2).

The total number of days in the regulatory review period which fall under paragraph (c)(1) is 1,485. Subtracting from this the number of days which were on or before the issue date of the patent leaves 740 days. Subtracting one-half of 740 from 1,820 leaves 1,450 days.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The number of days determined in paragraph (d)(1) depends upon whether the period from June 11, 2001 to February 25, 2003 falls under paragraph (c)(1) or paragraph (c)(2). Calculations for both of these alternatives are set out below.

(A) The period from June 11, 2001 to February 25, 2003 falls under paragraph (c)(1).

The number of days determined under paragraph (d)(1) is 1,138 days. Adding 1,138 days to the original term of U.S. Patent No. 5,843,901 results in a term extension to January 12, 2019.

(B) The period from June 11, 2001 to February 25, 2003 falls under paragraph (c)(2).

The number of days determined under paragraph (d)(1) is 1,450 days. Adding 1,450 days to the original term of U.S. Patent No. 5,843,901 results in a term extension to November 20, 2019.

- (3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;**

Adding 14 years to the date of approval of the NDA for Plenaxis™ results in an extension of the term of U.S. Patent No. 5,843,901 to November 25, 2017.

- (4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;**

The earlier of the expiration dates obtained pursuant to paragraphs (d)(2) and (d)(3) of §1.775 is November 25, 2017.

- (5) If the original patent was issued after September 24, 1984,**
(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and
(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

U.S. Patent No. 5,843,901 was issued after September 24, 1984. Adding 5 years to the original expiration date of U.S. Patent No. 5,843,901 results in a term extension to December 1, 2020. The earlier of the expiration dates determined according to paragraphs (d)(4) and (d)(5)(i) is November 25, 2017.

- (6) If the original patent was issued before September 24, 1984, and**
(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--
(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and
(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date;
(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--
(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer, and

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

The original patent issued after September 24, 1984. Thus, no adjustment of the term under paragraph (6) is required.

As set forth above, U.S. Patent No. 5,843,901 is eligible for a term extension of 725 days, with an expiration date of November 25, 2017.

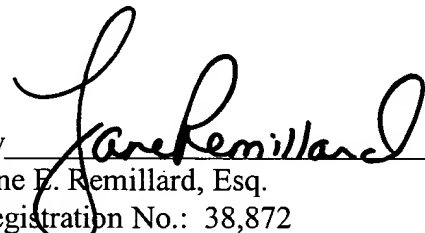
(13) Under 37 C.F.R. §1.165, Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The Commissioner is hereby authorized to charge the prescribed fee under 37 C.F.R. §1.20(j) for receiving and acting upon this application to our Deposit Account No. 12-0080. Please charge any additional fees or credit any overpayments associated with this communication to our Deposit Account No. 12-0080.

As required under 37 C.F.R. §1.740(b), five true copies of this application are enclosed.

Any inquiries and/or correspondence relating to this application for patent term extension should be directed to the undersigned.

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Date:

January 9, 2004

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EXHIBITS

- Exhibit A Copy of U.S. Patent No. 5,843,901
- Exhibit B Maintenance Fee Receipt
- Exhibit C FDA Letter of 10/22/96 Acknowledging Receipt of IND Application
- Exhibit D FDA Letter of 1/8/01 Acknowledging Receipt of NDA
- Exhibit E FDA Letter of 3/18/03 Acknowledging Receipt of NDA Resubmission
- Exhibit F FDA Letter of 11/25/03 Granting Marketing Approval
- Exhibit G Assignment document from Indiana University Foundation to Advanced Research and Technology Institute
- Exhibit H Power of Attorney document from Advanced Research and Technology Institute
- Exhibit I Power of Attorney from PRAECIS PHARMACEUTICALS INCORPORATED



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January 9, 2004

MailStop Patent Ext.
Commissioner for Patents
P.O. Box 1450
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Re: U.S. Patent No. 5,843,901 Issued: December 1, 1998
Title: "LHRH Antagonist Peptides"
Inventors: Roger W. Roeske
Attorney Docket No. PPI-007

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

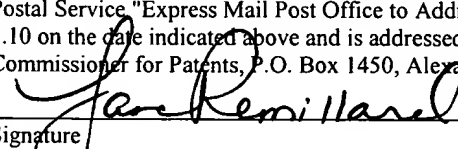
1. Application for Patent Term Extension Pursuant To 37 U.S.C. §156 and 37 C.F.R. §1.740, including Exhibits A-I:

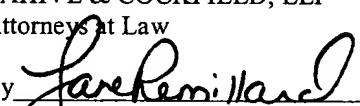
- Exhibit A - Copy of U.S. Patent No. 5,843,901;
- Exhibit B - Maintenance Fee Receipt;
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- Exhibit G - Assignment document from Indiana University Foundation to Advanced Research and Technology Institute;
- Exhibit H - Power of Attorney document from Advanced Research and Technology Institute;
- Exhibit I - Power of Attorney from PRAECIS PHARMACEUTICALS INCORPORATED;

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to MailStop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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US005843901A

United States Patent [19]
Roeske

[11] **Patent Number:** **5,843,901**
[45] **Date of Patent:** **Dec. 1, 1998**

[54] **LHRH ANTAGONIST PEPTIDES**[75] **Inventor:** Roger W. Roeske, Indianapolis, Ind.[73] **Assignee:** Advanced Research & Technology
Institute, Bloomington, Ind.[21] **Appl. No.:** 480,494[22] **Filed:** Jun. 7, 1995[51] **Int. Cl.**⁶ A61K 38/00; A61K 38/04;
A61K 38/08[52] **U.S. Cl.** 514/15; 514/2; 530/328[58] **Field of Search** 514/15; 530/328[56] **References Cited****U.S. PATENT DOCUMENTS**

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(List continued on next page.)

Primary Examiner—Cecilia J. Tsang*Assistant Examiner*—Michael Borin*Attorney, Agent, or Firm*—Lahive & Cockfield LLP; Giulio A. DeConti, Jr.; Catherine J. Kara[57] **ABSTRACT**

Novel LHRH antagonist peptides, pharmaceutical compositions thereof, and methods of use thereof, are disclosed.

5 Claims, No Drawings

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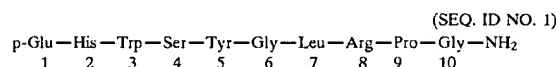
LHRH ANTAGONIST PEPTIDES

This invention was made with Government support under contract N01-HD-3-3172 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

The present invention relates to LHRH antagonist peptides and uses thereof.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are hormones released by the pituitary gland. These hormones regulate the functioning of the gonads and the production and maturation of gametes. LH and FSH are generally released by the pituitary gland upon prior release of triggering hormone from the hypothalamus. Luteinizing hormone-releasing hormone (LHRH; also known as gonadotropin-releasing hormone or GnRH) is one of the principal hypothalamic hormones which triggers the release of LH. Thus, release of LHRH represents a control point in the physiological regulation of gonadal function. The structure of mammalian LHRH has been determined, and has been found to be a decapeptide:



LH release is necessary for ovulation; thus, compounds which inhibit LH release by blocking the action of LHRH are useful as contraceptive agents. LHRH antagonists are also useful for regulating secretion of gonadotropins in male mammals, and thus can be used as male contraceptives. In addition, LHRH antagonists can be used in the treatment of sex-hormone dependent cancers (for example, prostate cancer), where increased levels of gonadotropins increase the rate of tumor growth.

Many modified LHRH analog peptides have been synthesized in an attempt to increase the potency of the antagonists, preferably while also increasing the resistance of the antagonist to enzymatic degradation. For example, synthetic LHRH antagonist peptides which incorporate modified or unnatural amino acids have been tested. Common substitutions include, for example, substitution of 4-Cl-D-Phe for His at position 2, or substitution of D-Ala-NH₂ for Gly-NH₂ at position 10.

One problem frequently encountered in LHRH antagonist peptides is the occurrence of histamine-releasing activity. This histamine-releasing activity represents a serious obstacle to the clinical use of such antagonists because histamine release results in adverse side effects such as edema and itching. Thus, LHRH antagonist peptides which have low histamine releasing activity are particularly desirable. Although the LHRH antagonist and histamine-releasing properties are not necessarily related, very few prior art compounds combine low histamine-releasing activity with high LHRH antagonist activity. Many prior art LHRH antagonist peptides also suffer from poor water-solubility, which complicates formulation of the antagonist for administration.

SUMMARY

The present invention features LHRH antagonist peptides, methods of modulating LHRH activity, and methods of treating a subject with the antagonists of the invention. In one aspect, the invention provides an LHRH antagonist,

comprising a peptide having a sidechain modified by a dipolar moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

In another aspect, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a cationic moiety selected from the group consisting of cationic pyridinium moieties and sulfonium moieties, with the proviso that the cationic moiety is not N-methyl pyridinium, forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

In another aspect, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a receptor-modifying moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

In still another aspect, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a hydrophilic N-acyl moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

In yet another aspect, the invention provides an LHRH antagonist, comprising a peptide having a small polar moiety in position 6, such that the peptide has LHRH antagonist activity.

In still further aspects, the invention provides pharmaceutical compositions of the LHRH antagonist peptides.

In another aspect, the invention provides a method of inhibiting LHRH activity in a subject, comprising administering to a subject an effective amount of an LHRH antagonist, such that LHRH activity is inhibited.

In another aspect, the invention provides a method of inhibiting LHRH activity in a cell, comprising contacting a cell with an LHRH antagonist, such that LHRH activity is inhibited.

In another aspect, the invention provides a method of inhibiting growth of a hormone-dependent tumor in a subject, comprising administering to a subject an effective amount of an LHRH antagonist, such that tumor growth is inhibited.

In another aspect, the invention provides a method of inhibiting ovulation in a subject, comprising administering to a subject an effective amount of an LHRH antagonist, such that ovulation is inhibited.

In another aspect, the invention provides a packaged formulation for treating a subject for a disorder associated with LHRH activity, comprising an LHRH antagonist packaged with instructions for using the LHRH antagonist for treating a subject having a disorder associated with LHRH activity.

DETAILED DESCRIPTION

In order that the present invention may be more readily understood, certain terms are first defined.

As used herein, "LHRH antagonist peptide" means a peptide or peptide analog which inhibits LHRH activity (i.e., has "LHRH antagonist activity") in vivo or in vitro. Candidate LHRH antagonist peptides can be assayed in the animal model described in Corbin and Beattie, *Endocrine Res. Commun.* 2:1 (1975) (and see infra). In this assay, the LHRH antagonistic activity of a candidate compound is assayed by measuring the antiovaratory activity (AOA) of the compound in rats.

The term "histamine-releasing activity", as used herein, refers to the tendency of a compound to release histamine when administered to a subject. The histamine-releasing

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activity of a compound can be measured with an *in vitro* assay (described in more detail, *infra*). Preferred LHRH antagonist peptides have high activity in the rat antiovulatory activity assay, but low histamine releasing activity. Preferred LHRH antagonist peptides have an ED_{50} in the histamine release assay of at least 3 $\mu\text{g}/\text{ml}$, more preferably at least 5 $\mu\text{g}/\text{ml}$, and still more preferably at least 10 $\mu\text{g}/\text{ml}$.

The term "alkyl", as used herein, refers to a straight or branched chain hydrocarbon group having from about 1 to about 10 carbon atoms. The term "lower alkyl" refers to an alkyl group having from about 1 to about 6 carbon atoms. Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, and n-hexyl. An alkyl group may be unsubstituted, or may be substituted at one or more positions, with, e.g., halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, heterocycles, hydroxyls, aminos, nitros, thiols, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like. Preferred alkyls are lower alkyls.

The term "cycloalkyl" refers to a cyclic saturated hydrocarbon group having from 3 to 8 carbon atoms. Exemplary cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Cycloalkyl groups may be unsubstituted or substituted at one or more ring positions as described for alkyls. Thus, a cycloalkyl may be substituted with, e.g., halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, heterocycles, hydroxyls, aminos, nitros, thiols, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like.

The terms "alkenyl" and "alkynyl", as used herein, refer to unsaturated groups analogous in length and possible substitution to the alkyls described above, but which contain at least one carbon-carbon double or triple bond respectively.

The term "aryl" as used herein includes 4-, 5-, 6- and 7-membered single-ring aromatic groups which may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycle" or "heteroaromatic". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, heterocycles, hydroxyls, aminos, nitros, thiols, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like. An aromatic ring may also be substituted with another aromatic ring, as in, for example, a biphenyl. Aryl groups also include fused or polycyclic aromatic systems.

The terms "heterocycle" or "heterocyclic group" refer to 4- to 10-membered ring structures, more preferably 5 to 7 membered rings, which ring structures include one to four heteroatoms. Heterocyclic groups include pyrrolidine, oxolane, thiolane, imidazole, oxazole, piperidine, piperazine, morpholine. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, other heterocycles, hydroxyl, amino, nitro, thiol, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls,

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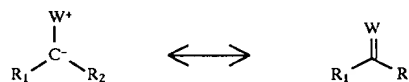
ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like. Heterocycles may also be bridged or fused to other cyclic groups as described below.

The terms "polycycle" or "polycyclic group" refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocycles) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, hydroxyl, amino, nitro, thiol, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur, phosphorus and selenium.

The term "arylalkyl", as used herein, refers to an aryl group appended to an alkyl group, including, but not limited to, benzyl, naphthylmethyl, pyridyl methyl, and the like.

The term "ylid" is known in the art and refers to a moiety in which a positively charged atom (especially from Groups V and VI of the periodic table) is bonded to a carbon atom which bears an unshared pair of electrons. Thus, an ylid has the resonance forms:



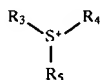
in which W is a heteroatom such as S, or P, and R_1 and R_2 are, independently, H, alkyl, cycloalkyls, alkenyl, alkynyl, aryl, alkoxy, thioalkoxy, and the like. The heteroatom is substituted with an appropriate number of substituents (i.e., two for N and S, and three for P); the substituents are independently alkyl, cycloalkyl, aryl, and the like. Nitrogen ylides do not have a significant contribution from the non-charge-separated resonance form (on the right, above).

The term "dipolar moiety", as used herein, refers to a covalently bonded moiety having both positive and negative charges (e.g., a zwitterionic moiety). Exemplary dipolar groups include ylids (e.g., of S, N, or P), tertiary amine oxides, nitrones, pyridine-N-oxides, nitrile oxides, quaternary amino acids (e.g., 2-(N,N,N-trialkylammonium) acetate), amino acids, sulfonium arene oxides (as described in, for example, U.S. Pat. No. 4,111,914), betaines (e.g., trigonellin), and the like. In certain preferred embodiments, the dipolar moiety is a pyridine-N-oxide. In other preferred embodiments, the dipolar moiety is a zwitterionic pyridinium moiety.

As used herein, a "cationic moiety" is a moiety in which at least one atom bears a positive charge, and the moiety has a net positive charge. Thus, for example, an N-alkyl (or N-alkenyl, -alkynyl, or -aryl, collectively referred to herein as "N-substituted pyridinium") pyridinium moiety can be a cationic moiety (and is referred to herein as a "cationic pyridinium moiety"), but a pyridine-N-oxide is not, unless it has a net positive charge. As described above, a pyridine-N-oxide can be a dipolar moiety. Other exemplary cationic moieties include quaternary amines, sulfonium salts, phosphonium salts, and the like. In certain preferred embodiments, the cationic moiety is a sulfonium moiety.

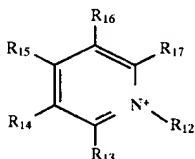
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A sulfonium moiety has the following structure:



in which R_3 , R_4 and R_5 are each, independently, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, and the like.

In other preferred embodiments, the cationic moiety is a cationic pyridinium moiety. A cationic pyridinium moiety has the following structure:



wherein R_{12} is alkyl or aryl, and R_{13} – R_{17} are each, independently, hydrogen, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, other heterocycles, hydroxyl, amino, nitro, thiol, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like. Preferred cationic pyridinium moieties include Pal(iPr) and Pal(Bzl). N-methyl pyridinium moieties are not preferred.

Although the above examples describe pyridine (or pyridinium) moieties, it will be apparent to the skilled artisan that other N-heteroaromatic moieties (that is, a moiety in which at least one nitrogen is present in an aromatic ring) may be substituted for the pyridine (or pyridinium) moieties described herein. Exemplary N-heteroaromatics include thiazole, triazole, tetrazole, pyrazole, pyrazine, pyridazine and pyrimidine, and the like. Thus, N-substituted pyrazines, pyridazines, and the like, are contemplated for use in the present invention.

As used herein, "tertiary amine" includes trialkyl amines, triaryl amines, and amines which have both alkyl and aryl substituents.

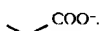
As used herein, "zwitterionic pyridinium moiety" refers to a moiety having the form:



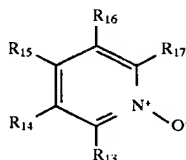
in which R_6 comprises an alkyl, cycloalkyl, alkenyl, alkynyl, or aryl moiety, and R_7 – R_{11} are each, independently, hydrogen, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, other heterocycles, hydroxyl, amino, nitro, thiol, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $-\text{CF}_3$, $-\text{CN}$, or the like, with the proviso that at least one of R_6 – R_{11} is substituted with an anionic moiety. An "anionic moiety", as used herein, is a moiety which has a net negative charge. The anionic moiety is chosen to be compatible with other moieties, and to form a stable compound. Illustrative anionic moieties include carboxylates, phosphates, phosphonates, sulfates, sulfonates, and the like. In certain preferred embodiments, the anionic moiety is a carboxylate. In other

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preferred embodiments, the anionic moiety is a sulfonate. In a preferred embodiment, R_6 comprises:

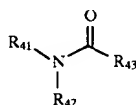


A pyridine N-oxide is a moiety which has the form:



where R_{13} – R_{17} have the meanings defined above.

The term "hydrophilic N-acyl moiety", as used herein, refers to a moiety which comprises a nitrogen atom acylated so as to form a hydrophilic moiety. Thus, a hydrophilic N-acyl moiety can have the form:



where R_{41} and R_{42} are each, independently, H, alkyl, cycloalkyl, aryl and the like; and R_{43} is alkyl, cycloalkyl, alkenyl, alkynyl, aryl, and the like; and R_{41} – R_{43} are selected to form a hydrophilic moiety. In preferred embodiments, R_{41} and R_{42} are not both H.

Relative hydrophilicity can be determined by any of several methods known in the art (Hansch, ed., "Comprehensive Medicinal Chemistry", Vol. 4, Pergamon Press, Oxford, 1990), and can be used to guide the choice of potential hydrophilic moieties for use in the invention. The partition coefficient, P , between 1-octanol and water has been used as a reference for measuring the hydrophilicity of a compound. Hydrophilicity can be expressed as $\log P$, the logarithm of the partition coefficient (Hansch et al., *Nature* 194:178 (1962); Fujita et al., *J. Am. Chem. Soc.* 86:5175 (1964)). Standard tables of hydrophilicity for many molecules, and lipophilicity (hydrophobicity) substituent constants (denoted π) for many functional groups, have been compiled (see, e.g., Hansch and Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," Wiley, New York, N.Y., (1979)). The hydrophilicity of a vast range of candidate hydrophilicity moieties can be quite accurately predicted with the aid of these tables. For example, the measured $\log P$ (octanol/water) of naphthalene is 3.45. The substituent constant p for $-\text{OH}$ is -0.67 . Therefore, the predicted $\log P$ for β -naphthol is $3.45 + (-0.67) = 2.78$. This value is in good agreement with the measured $\log P$ for β -naphthol, which is 2.84. In certain preferred embodiments, the hydrophilic N-acyl moiety has a value of $\log P$ between -1 and $+2$, more preferably between -0.5 and $+1.5$. Examples of residues incorporating preferred hydrophilic acyl moieties are D-Lys(Imdac), D-Lys(Ppic) and D-Lys(Dodac). Even more preferred residues incorporating hydrophilic acyl moieties include Lys(pGlu), Lys(Otac), and Lys(Onic).

The term "small polar moiety" refers to a moiety which has small steric bulk and is relatively polar. Polarity is measured as hydrophilicity by the P scale described above. In certain preferred embodiments, the small polar moieties have a $\log P$ between -1 and $+2$. In particularly preferred

embodiments, the small polar moiety modifies residue 6. In preferred embodiments, the steric bulk of the small polar moiety is less than the steric bulk of Trp. Examples of residues incorporating preferred small polar moieties are D- or L-Cit, D- or L-Asn, D- or L-Gln, and D- or L-Thr. In preferred embodiments, the small polar moiety is not Glu or a carboxylic ester of Glu.

The term "leaving group" is known in the art and, as used herein, refers to a functionality which upon heterolytic bond cleavage departs with an electron pair. In general, good leaving groups are those moieties which are expelled from the substrate as weak bases, whether charged or uncharged. For example, sulfates, sulfonates, sulfides, chloride, bromide, iodide, phosphates, phosphinates, and the like are good leaving groups. In other words, when, for example, a C—S bond of a sulfonium moiety is cleaved, a sulfide departs (with an electron pair).

The term "receptor-modifying moiety", as used herein, refers to a moiety which can modify, covalently or non-covalently, a receptor for an LHRH antagonist peptide. For example, it has recently been shown (C. A. Flanagan et al., (1994) *J. Biol. Chem.* 269:22636) that Glu301 of the mouse LHRH receptor (which corresponds to Asp301 in the human LHRH receptor) interacts with Arg⁸ in LHRH agonists. Thus, a carboxylate-modifying reagent (such as an alkylating agent) can modify Glu301 (Asp301) and thus modify the mouse (or human) LHRH receptor. A receptor-modifying moiety may act to bond the LHRH antagonist peptide to the receptor (e.g., esterifying the antagonist to the receptor by displacement of a leaving group), or it may modify the receptor without bonding the LHRH antagonist peptide to the receptor (e.g., by methylation with a methylsulfonium moiety). Other residues of an LHRH receptor can also be modified, and moieties which can modify such residues are also receptor-modifying moieties. Exemplary receptor-modifying reagents include alkyl and benzyl halides (e.g., methyl iodide or benzyl bromide), α -haloketones, α -haloesters and α -haloamides (collectively referred to as " α -halocarboxyls"), sulfonium salts, sulfates, alkyl or aryl sulfonates, and other reagents which comprise a good leaving group as described above. Other receptor-modifying reagents are described in, for example, A. J. Barrett and G. Salvesen, eds. (1986) "Proteinase Inhibitors", *Research Monographs in Cell and Tissue Physiology*, Vol. 12, Elsevier Press, Amsterdam.

Although in certain embodiments an LHRH antagonist of the invention contains a receptor-modifying moiety, the invention is not intended to be limited to those antagonists that actually modify a receptor residue. An LHRH antagonist comprising a receptor-modifying moiety but which does not actually modify the receptor may nonetheless be an effective LHRH antagonist. However, for those antagonists that do modify a receptor residue, one advantage is that such moieties can be designed to selectively modify only the targeted receptor, thereby reducing non-specific reactions and decreasing the probability of toxic side effects.

The term "a peptide having a sidechain modified by" a moiety, as used herein, refers to a peptide (or peptide mimetic, see below) in which at least one residue has a sidechain comprising that moiety. Thus, for example, a "peptide having a sidechain modified by a dipolar moiety" means a peptide in which at least one side chain comprises a dipolar moiety.

The LHRH antagonist peptides of the present invention also include peptide analogs and peptide mimetics. The terms "peptide analog", "peptide derivative" and "peptide mimetic" as used herein are intended to include molecules

which mimic the chemical structure of a peptide and retain the functional properties of the peptide. A "residue" refers to an amino acid or amino acid mimetic incorporated in the peptide compound by an amide bond or amide bond mimetic. Approaches to designing peptide analogs are known in the art. For example, see Farmer, P. S. in *Drug Design* (E. J. Ariens, ed.) Academic Press, New York, 1980, vol. 10, pp. 119–143; Ball, J. B. and Alewood, P. F. (1990) *J. Mol. Recognition* 3:55; Morgan, B. A. and Gainor, J. A. (1989) *Ann. Rep. Med. Chem.* 24:243; and Freidinger, R. M. (1989) *Trends Pharmacol. Sci.* 10:270.

An "amino acid mimetic" refers to a moiety, other than a naturally occurring amino acid, that conformationally and functionally serves as a substitute for a particular amino acid in a peptide compound without adversely interfering to a significant extent with the function of the peptide (e.g., interaction of the peptide with an LHRH receptor). In some circumstances, substitution with an amino acid mimetic may actually enhance properties of the peptide (e.g., interaction of the peptide with an LHRH receptor). Examples of amino acid mimetics include D-amino acids. LHRH antagonist peptides substituted with one or more D-amino acids may be made using well known peptide synthesis procedures. The effect of amino acid substitutions with D-amino acids or other amino acid mimetics can be tested using assays, e.g., the AOA and histamine-release assays as described below. Other methods of determining the effect of substitution with an amino acid mimetic will be apparent to the skilled artisan.

The peptide analogs or mimetics of the invention include isosteres. The term "isostere" as used herein refers to a sequence of two or more residues that can be substituted for a second sequence because the steric conformation of the first sequence fits a binding site specific for the second sequence. The term specifically includes peptide back-bone modifications (i.e., amide bond mimetics) well known to those skilled in the art. Such modifications include modifications of the amide nitrogen, the α -carbon, amide carbonyl, complete replacement of the amide bond, extensions, deletions or backbone crosslinks. Several peptide backbone modifications are known, including ψ [CH₂S], ψ [CH₂NH], ψ [C(S)NH₂], ψ [NHCO], ψ [C(O)CH₂], and ψ [(E) or (Z) CH=CH]. In the nomenclature used above, ψ indicates the absence of an amide bond. The structure that replaces the amide group is specified within the brackets. Other examples of isosteres include peptides substituted with one or more benzodiazepine molecules (see e.g., James, G. L. et al. (1993) *Science* 260:1937–1942).

Other possible modifications include an N-alkyl (or aryl) substitution (ψ [CONR]), backbone crosslinking to construct lactams and other cyclic structures, or retro-inverso amino acid incorporation (ψ [NHCO]). By "inverso" is meant replacing L-amino acids of a sequence with D-amino acids, and by "retro-inverso" or "enantio-retro" is meant reversing the sequence of the amino acids ("retro") and replacing the L-amino acids with D-amino acids. For example, if the parent peptide is Thr-Ala-Tyr, the retro modified form is Tyr-Ala-Thr, the inverso form is thr-ala-tyr, and the retro-inverso form is tyr-ala-thr (lower case letters refer to D-amino acids). Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide and is able to bind the selected LHRH receptor. See Goodman et al. "Perspectives in Peptide Chemistry" pp. 283–294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

In addition to amino acid-substituted LHRH antagonist peptides, the invention also encompasses LHRH antagonist peptide compounds having other modifications. For example, the amino-terminus or carboxy-terminus of the peptide can be modified. The term "amino-derivative group" is intended to include amino-terminal modifications of the peptide compounds of the invention. Examples of N-terminal modifications include alkyl, cycloalkyl, aryl, arylalkyl, and acyl groups. A preferred N-terminal modification is acetylation. The N-terminal residue may be linked to a variety of moieties other than amino acids such as polyethylene glycols (such as tetraethylene glycol carboxylic acid monomethyl ether), pyroglutamic acid, succinoyl, methoxy succinoyl, benzoyl, phenylacetyl, 2-, 3-, or 4-pyridylalkanoyl, aroyl, alkanoyl (including acetyl and cycloalkanoyl e.g., cyclohexylpropanoyl), arylalkanoyl, arylaminocarbonyl, alkylaminocarbonyl, cycloalkylaminocarbonyl, alkyloxycarbonyl (carbamate caps), and cycloalkoxycarbonyl, among others.

The term "carboxy-derivative group" is intended to include carboxy-terminal modifications of the peptide compounds of the invention. Examples of modifications of the C-terminus include modification of the carbonyl carbon of the C-terminal residue to form a carboxyterminal amide or alcohol (i.e., a reduced form). In general, the amide nitrogen, covalently bound to the carbonyl carbon on the C-terminal residue, will have two substitution groups, each of which can be hydrogen, alkyl or an alkylaryl group (substituted or unsubstituted). Preferably the C-terminal is an amido group, such as $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CONHCH}_2\text{C}_6\text{H}_5$ or $-\text{CON}(\text{CH}_3)_2$, most preferably $-\text{CONH}_2$, but may also be 2-, 3-, or 4-pyridylmethyl, 2-, 3-, or 4-pyridylethyl, carboxylic acid, ethers, carbonyl esters, alkyl, arylalkyl, aryl, cyclohexylamide, piperidineamide, other mono or disubstituted amides, ureas, or carbamates. Other moieties that can be linked to the C-terminal residue include piperidine-4-carboxylic acid or amide and cis- or trans-4-amino-cyclohexanecarboxylic acid or amide.

The modified forms of LHRH antagonist peptides of the invention, including L- or D-amino acid substitutions, covalent modification of end termini or side chains, and peptide analogs and mimetics can be selected for desired alterations of the physical or chemical properties of the peptide, for example, increased stability, solubility, bioavailability, increased or decreased immunogenicity, etc. The peptides of the invention can be targeted to particular organs (e.g. the brain) by methods known in the art, for example, the dihydropyridine-pyridinium carrier of Bodor (see, e.g., U.S. Pat. No. 4,540,564). In an exemplary embodiment, when a side-chain modified by a pyridinium moiety is desired, the corresponding N-alkylated dihydropyridine sidechain is incorporated into the peptide. When the peptide is administered to a subject, the N-alkylated dihydropyridine sidechain is oxidized in vivo to the desired pyridinium moiety.

Preferred LHRH antagonist peptides of the present invention range in length from about 8 to about 12 residues, more preferably from 9 to 11 residues, and most preferably are 10 residues in length.

The LHRH antagonist peptides of the present invention can be prepared by any suitable method for peptide synthesis, including solution-phase and solid-phase chemical synthesis. Preferably, the peptides are synthesized on a solid support. Methods for chemically synthesizing peptides are well known in the art (see, e.g., Bodansky, M. *Principles of Peptide Synthesis*, Springer Verlag, Berlin (1993) and Grant, G. A. (ed.). *Synthetic Peptides: A User's Guide*, W.H. Freeman and Company, New York (1992). Automated peptide synthesizers are commercially available.

The use of combinatorial libraries to identify ligands is now well established (see, e.g., M. A. Gallop et al., (1994) *J. Med. Chem.* 37:1233; and E. M. Gordon et al., (1994) *J. Med. Chem.* 37:1385; and references cited therein). Therefore, LHRH antagonist peptides can be identified by chemical (e.g., solution or solid-phase) synthesis of combinatorial libraries (e.g., of peptides or peptoids) and screening of the resulting libraries according to known techniques. Thus, many potential ligands can be synthesized and screened in a short period of time, and the most active ligands selected for further testing or use.

Standard abbreviations and conventions are used throughout this disclosure when describing the peptides of the invention. Peptides are written with the N-terminus on the left, the carboxyl terminus on the right. Amino acids are of the L-form unless stated otherwise, e.g., D-Lys means the D-form of lysine. Ac-Xaa means the N-terminal residue Xaa is N-acetylated; C-terminal amides are denoted Xaa-NH₂. In Table 1, only residues which differ from native mammalian LHRH are noted; thus, the notation Met(S⁺Me)⁸-LHRH.TFA means a peptide which differs from native mammalian LHRH only in the substitution of Met(S⁺Me) for the native Arg at position 8 (TFA indicates the trifluoroacetate salt). Lys(iPr) denotes N-ε-2-propyl-lysine; other alkylating and acylating moieties are similar indicated. Thus, for example, Met(S+CH₂C₆H₅) denotes S-benzyl methionine. Certain other non-standard residues and moieties are abbreviated as follows:

Abbreviation	Residue or moiety
pGlu	pyro-glutamyl
Nal	3-(2-naphthyl)alaninyl
Ada	3-(1-adamantanyl)alaninyl
4-Cl-Phe	(4'-chlorophenyl)alaninyl
Qal	3-(2'-quinolinyl)alaninyl
Pal	3-(3'-pyridyl)alaninyl
Pal(N—O)	3-(3'-pyridine-N-oxide)alaninyl
Pal(iPr)	3-N-(2-propyl)-3'-pyridinium)alaninyl
Pal(Bzi)	3-N-(benzyl)-3'-pyridinium)alaninyl
Pal(CH ₂ COO ⁻)	3-(3'-pyridinium-N-(2-acetate)alaninyl
Lys(iPr)	N-ε-2-propyl-lysine
Imdac	2-oxo-4-imidazolyl
Otac	2-oxo-4-thiazolyl
Ppic	3-(piperidin-1-yl)-propanoyl
Dodac	2,5-dioxo-4-imidazolyl
Met(S ⁺ Me)	S-methyl methioninyl
PEG	polyethylene glycol
Cit	citrullinyl
Glu(Taurine)	5-(2-sulfoethylamido)glutamyl
Pyz	1,4-pyrazinecarbonyl
Pip	pipecolyl
CNa	(2-cyano)acetyl
Dea	diethylamide
Onic	3-nicotinyl-N-oxide
Glc	gluconate
Orotic	orotate
Orn	ornithine
Dap	2,4-diaminopropionyl

I. LHRH Antagonist Peptides of the Invention

In one aspect, the invention pertains to LHRH antagonist peptides.

In one embodiment, the invention provides a peptide comprising a structure:

A-B-C-D-E-F-G-H-I-J

(SEQ ID NO: 2)

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal
B is His or 4-Cl-D-Phe

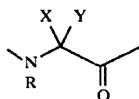
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C is Trp, D-Pal, D-Nal, L-Nal, D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is



wherein

R and X are, independently, H or alkyl; and

Y comprises a dipolar moiety;

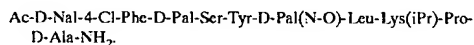
G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

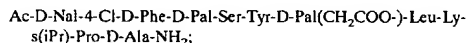
I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof. In preferred embodiments, Y is selected from the group consisting of ylids, tertiary amine oxides, nitrile oxides, pyridine-N-oxides, and pyridinium zwitterions. In particularly preferred embodiments, Y is an ylid, a pyridine-N-oxide or a pyridinium zwitterion. In a preferred embodiment, the peptide comprises a structure:

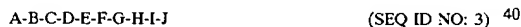


In a preferred embodiment, the peptide comprises a structure:



or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a peptide comprising a structure:



wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal

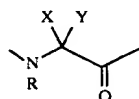
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal, D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is D-Arg, D-Lys(iPr), D-Pal(iPr), D-Cit or Q, wherein Q has a structure



wherein

R and X are, independently, H or alkyl; and

Z comprises a cationic moiety selected from the group consisting of cationic pyridinium moieties and sulfonium moieties, with the proviso that the cationic moiety is not N-methyl pyridinium;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, Arg or Q;

I is Pro; and

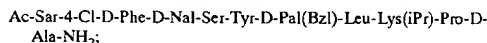
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J is Gly-NH₂ or D-Ala-NH₂;

with the proviso that at least one of F and H is Q; or a pharmaceutically acceptable salt thereof.

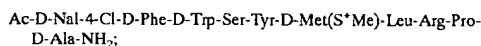
In preferred embodiments, F is Q and Z is a cationic pyridinium moiety. In preferred embodiments, Z is an N-benzyl pyridinium moiety. In other preferred embodiments, F is Q and Z is a sulfonium moiety. In yet other preferred embodiments, H is Q and Z is a sulfonium moiety.

In a particularly preferred embodiment, the peptide comprises a structure



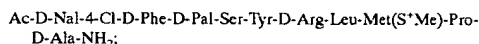
or a pharmaceutically acceptable salt thereof.

In a particularly preferred embodiment, the peptide comprises a structure:



or a pharmaceutically acceptable salt thereof.

In a particularly preferred embodiment, the peptide comprises a structure:



or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a peptide comprising a structure:



wherein

A is p-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal

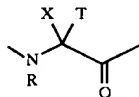
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal, D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is



wherein

R and X are, independently, H or alkyl; and

T comprises a receptor-modifying moiety;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

In preferred embodiments, T is selected from the group consisting of ylids, sulfonium moieties, α-halocarbonyls, sulfates, sulfonates, alkyl halides and benzyl halides. In a particularly preferred embodiment, T is an α-halocarbonyl.

In another embodiment, the invention provides a peptide comprising a structure:



wherein

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A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal

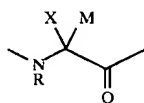
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal, D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is



wherein

R and X are, independently, H or alkyl; and

M comprises an N-acyl hydrophilic moiety;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a peptide comprising a structure:

A-B-C-D-E-F-G-H-I-J

(SEQ ID NO: 6)

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal

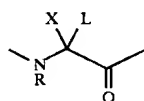
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal, D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is



wherein

R and X are, independently, H or alkyl; and

L comprises a small polar moiety;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

I is Pro; and

J is Gly-NH₂ or D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

In preferred embodiments, F is selected from the group consisting of D-Cit, D-Asn, D-Gln, and D-Thr. In a particularly preferred embodiment, the peptide comprises a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-N-Me-Tyr-D-Asn-Leu-Lys(iPr)-Pro-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

In another particularly preferred embodiment, the peptide comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-NH₂;

or a pharmaceutically acceptable salt thereof.

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In another aspect, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a dipolar moiety forming a modified peptide, such that the modified peptide has FHRH antagonist activity. In preferred embodiments, the dipolar moiety is selected from the group consisting of ylids, tertiary amine oxides, nitrile oxides, pyridine-N-oxides, and pyridinium zwitterions. In more preferred embodiments, the dipolar moiety is an ylid, a pyridine-N-oxide or a pyridinium zwitterion. In other preferred embodiments, the peptide comprises about 8 to about 12 residues. In more preferred embodiments, the peptide comprises 10 residues. In certain preferred embodiments, the dipolar moiety modifies residue 6. In certain preferred embodiments, the LHRH antagonist is a peptide mimetic.

In another embodiment, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a cationic moiety selected from the group consisting of cationic pyridinium moieties and sulfonium moieties, with the proviso that the cationic moiety is not N-methyl pyridinium, forming a modified peptide, such that the modified peptide has LHRH antagonist activity. In preferred embodiments, the cationic moiety is a cationic pyridinium moiety. In other preferred embodiments, the cationic moiety is a sulfonium moiety. In other preferred embodiments, the peptide comprises about 8 to about 12 residues. In more preferred embodiments, the peptide comprises 10 residues. In other preferred embodiments, the cationic moiety modifies at least one of residue 6 and residue 8. In other preferred embodiments, the LHRH antagonist is a peptide mimetic.

In another embodiment, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a receptor-modifying moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity. In preferred embodiments, the receptor-modifying moiety is selected from the group consisting of ylids, sulfonium moieties, α -halocarbonyls, sulfates, sulfonates alkyl halides, and benzyl halides. In preferred embodiments, the peptide comprises about 8 to 12 residues. In more preferred embodiments, the peptide comprises 10 residues. In preferred embodiments, the receptor-modifying moiety modifies residue 6. In preferred embodiments, the LHRH antagonist is a peptide mimetic.

In another embodiment, the invention provides an LHRH antagonist, comprising a peptide having a sidechain modified by a hydrophilic N-acyl moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity. In preferred embodiments, the hydrophilic N-acyl moiety modifies position 6. In preferred embodiments, a residue comprises a hydrophilic acyl moiety is selected from the group consisting of D-Lys(Imdac), D-Lys(Ppic), and D-Lys(Dodac). In preferred embodiments, the hydrophilic N-acyl moiety has a log P between -1 and +2.

In another embodiment, the invention provides an LHRH antagonist, comprising a peptide having a small polar moiety in position 6, such that the peptide has LHRH antagonist activity. In preferred embodiments, the antagonist has an AOA less than about 1 μ g. In preferred embodiments, the antagonist has a histamine-releasing activity of at least about 5 μ g.

II. Pharmaceutical Compositions

The LHRH antagonist peptides of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. In a preferred embodiment, the pharmaceutical composition comprises an LHRH antagonist peptide of the invention and a pharmaceutically acceptable carrier.

A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired result. A therapeutically effective amount of an LHRH antagonist peptide of the present invention may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antagonist to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antagonist are outweighed by the therapeutically beneficial effects. A non-limiting range for a therapeutically effective amount of an LHRH antagonist is 0.01 $\mu\text{g/kg}$ -10 mg/kg, preferably between about 0.01 and 5 mg/kg. It is to be noted that dosage values may vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous or parenteral administration (e.g., by injection). Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound.

A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects. Examples of such salts are salts of acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like; acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, benzoic acid, pamoic acid, alginic acid, methanesulfonic acid, naphthalene-sulfonic acid, and the like. Also included are salts of cations such as sodium, potassium, lithium, zinc, copper, barium, bismuth, calcium, and the like; or organic cations such as trialkylammonium. Combinations of the above salts are also useful.

The LHRH antagonists of the present invention can be administered by a variety of methods known in the art. In a preferred embodiment, the LHRH antagonists are administered in a time release formulation, for example in a composition which includes a slow release polymer, or by depot injection. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

The LHRH antagonists can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The LHRH antagonists and other ingredients may also be enclosed in a hard or soft shell gelatin capsule,

compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the LHRH antagonists may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the LHRH antagonists in the compositions and preparations may, of course, be varied. The amount of the LHRH antagonists in such therapeutically useful compositions is such that a suitable dosage will be obtained.

To administer the LHRH antagonists by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the LHRH antagonists may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., (1984) *J. Neuroimmunol.* 71:27). Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., LHRH antagonist) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form

as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

III. Methods of Using the LHRH Antagonists of the Invention

The LHRH antagonist peptides of the present invention are useful for the treatment of such conditions as precocious puberty, prostate cancer, ovarian cancer, benign prostatic hypertrophy, endometriosis, uterine fibroids, breast cancer, premenstrual syndrome, polycystic ovary syndrome, and diseases which result from excesses of gonadal hormones in humans or animals of either sex. The LHRH antagonist peptides of the invention are also useful for behavior modification (e.g., "chemical castration"). The LHRH antagonist peptides are also useful for controlling reproduction in both males and females. Furthermore, the peptides of the invention may be used to treat immunosuppressed patients, as described in, for example, U.S. Pat. No. 5,003,011.

Thus, in one embodiment, the invention provides a method of inhibiting LHRH activity in a subject, comprising administering to a subject an effective amount of an LHRH antagonist of the present invention, such that LHRH activity is inhibited.

In another embodiment, the invention provides a method of inhibiting LHRH activity in a cell, comprising contacting a cell with an LHRH antagonist of the invention, such that LHRH activity is inhibited.

In another embodiment, the invention provides a method of inhibiting growth of a hormone-dependent tumor in a subject, comprising administering to a subject an effective amount of an LHRH antagonist of the invention, such that tumor growth is inhibited.

In another embodiment, the invention provides a method of inhibiting ovulation in a subject, comprising administering to a subject an effective amount of an LHRH antagonist of the invention, such that ovulation is inhibited.

In another aspect, the invention provides a packaged formulation for treating a subject for a disorder associated with LHRH activity, comprising an LHRH antagonist of the invention packaged with instructions for using the LHRH antagonist for treating a subject having a disorder associated with LHRH activity.

Exemplification

In the examples, the following abbreviations are used:

Boc: N-t-butoxycarbonyl

HOBt: 1-hydroxybenzotriazole

MCPBA: m-chloroperbenzoic acid

DCC: dicyclohexylcarbodiimide

Anti-ovulatory activity (AOA) was measured by an in vivo assay in rats, as described in Corbin and Beattie, *Endocrine Res. Commun.* 2:1 (1975). In brief, female rats are injected with a candidate LHRH antagonist on the day of proestrus; in general, the candidate LHRH antagonist was dissolved in 0.1% DMSO. The ability of the candidate peptide to inhibit ovulation is measured by determining the number of rats which ovulate. A candidate peptide is con-

sidered to have LHRH antagonist qualities if it inhibits ovulation in at least 50% of the treated rats at a dose of 5 µg per rat. Preferred LHRH antagonists inhibit ovulation in at least 50% of rats at a dose of 2 µg per rat, more preferably at a dose of 1 µg per rat, and still more preferably at a dose of 0.5 µg per rat.

Histamine-releasing activity was assayed by the method described in U.S. Pat. No. 4,851,385 to Roeske. Briefly, a suspension of rat mast cells was added to increasing concentrations of an LHRH antagonist peptide and incubated for 15 minutes at 37° C. The buffer contained 25 mM PIPES, pH 7.4, NaCl (119 mM), KCl (5 mM), NaOH (40 mM) glucose (5.6 mM), CaCl₂ (1 mM) and 0.1% bovine serum albumin. The reaction was stopped by centrifugation at 400x g for 15 minutes at 4° C., and the supernatant assayed for histamine content by a published method (Siriganian (1974) *Anal. Biochem.* 57:383 and Siriganian and Hook (1986) in "Manual of Clinical Immunology", 3rd ed., N. R. Rose, H. Friedman, and J. L. Fahey, eds., p. 808), or by a manual method which gave similar results. Maximal histamine release occurred rapidly, typically in less than one minute. No evidence of cell toxicity was seen for any of the peptides tested. The histamine-releasing activity of peptides is measured as the ED₅₀, in µg/ml; a higher ED₅₀ represents lower histamine release.

The AOA and histamine-releasing activities of several peptides are summarized in Table 1.

TABLE I

LHRH Antagonists		AO activity (AOA)	Histamine release
Compound	Sequence		
3341	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Gln ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	4/10 @ 1 µg 2/10 @ 2 µg	106
3342	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Asn ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	2/10 @ 2 µg	126
3343	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Thr ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	5/10 @ 1 µg	62
3344	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ , Pip ⁹ -D-Ala ¹⁰ -LHRH.TFA	9/10 @ 1 µg	32
3361	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Glu(Taurine) ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	1/8 @ 5 µg	131
3362	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ -LHRH.TFA	4/8 @ 1 µg	22
3363	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ , Pip ⁹ -LHRH.TFA	6/8 @ 1 µg	25
3364	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Phe(4-NO ₂) ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	6/8 @ 1 µg	14
3365	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ , ProNHEt ⁶ -des-Gly ¹⁰ -LHRH.TFA		24
3366	Ac-D-(or L)-9-anthryl-Ala ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	6/8 @ 5 µg	
3367	Ac-L-(or D)-9-anthryl-Ala ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	7/8 @ 5 µg	
3368	Ac-D-(or L)-Ada-Ala ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Cit ⁶ -Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	5/8 @ 5 µg	34

TABLE I-continued

LHRH Antagonists		AO activity (AOA)	Hista- mine release
Com- pound	Sequence		
3369	Ac—L-(or D)-Ada—Ala ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Cit ⁶ —Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 5 µg	93
3423A	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Glc) ⁶ —Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/10 @ 0.5 µg 2/10 @ 1 µg 0/10 @ 2 µg 1/8 @ 1 µg	52
3428	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Pal(1-Bu) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3429	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Pal(Bzl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	0/8 @ 1 µg 4/8 @ 0.5 µg	6.0
3430	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Pal ² , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	3/8 @ 1 µg	10
3431	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Cit ⁶ , D—Cit ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1 µg	
3432	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Pal ² , D—Cit ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1 µg	
3433	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Cit ⁶ , D—Pal ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	5/8 @ 1 µg	
3434	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Asn ⁶ , Tyr ⁶ , D—Cit ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	4/8 @ 1 µg	
3435	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Cit ⁶ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1 µg	
3436	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—HomoArg(NO ₂) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1 µg	
3437	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Glycolyl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1 µg	
3438	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	2/8 @ 1 µg	5.6
3439	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(HomoPro) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	2/8 @ 1 µg	
2958	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3440	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(3-pyridineacetic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	2/8 @ 1 µg	
3441	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(2-ClNic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	8/8 @ 1 µg	
3442	Ac—N ^o Me—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Cit ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1 µg	
3502	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Otac) ⁶ , D—Lys(Otac) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1 µg	
3503	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(ONic) ⁶ , D—Lys(ONic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1 µg	
3504	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Pyz) ⁶ , D—Lys(Pyz) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	4/8 @ 1 µg	
3552	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	8/8 @ 1 µg	
3505	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	5/8 @ 1 µg	

TABLE I-continued

LHRH Antagonists		AO activity (AOA)	Hista- mine release
Com- pound	Sequence		
3506	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Gulonyl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	4/8 @ 1 µg	
3553	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(iPrNic) ⁶ , D—Lys(iPrNic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	8/8 @ 1 µg	
3507	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(ONic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	1/8 @ 1 µg	
3508	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(OTac) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	0/8 @ 1 µg 6/8 @ 0.5 µg	
3509	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Pyz) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3510	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(nBuNic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3511	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(Amp) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1 µg	
3543	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(Dea) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1 µg	
3563	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(pGlu) ⁶ , D—Lys—Glu ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3540	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , N ^o Me—Tyr ⁶ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3541	Ac—D—Nal ¹ , C ^o Me—4Cl—Phe ² , D—Pal ³ , N ^o Me—Tyr ⁶ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	1/8 @ 1 µg	
3554	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(CNa) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA		
3542	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(PEG) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 2 µg	
3565	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Oxa) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA		
3551	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(CNa) ⁶ , D—Lys(CNa) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1 µg	
3544	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(CINic) ⁶ , D—Lys(CINic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1 µg	
3555A	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Ac) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA		
3564	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(Tris) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA		
3545	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Gln(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 1 µg	
3550	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(CSer) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1 µg	
3549	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(Mop) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1 µg	
3548	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys ⁶ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.4TFA	6/8 @ 1 µg	
3566	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Nic) ⁶		

TABLE I-continued

LHRH Antagonists			
Compound	Sequence	AO activity (AOA)	Histamine release
3567	D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
3568	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Ac) ⁵ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
3547	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Glu(DEGA) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1 μg	
3569	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Nic) ⁵ , D—Pal(Bzl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
3546	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Ac) ⁵ , D—Pal(Bzl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA	6/8 @ 1 μg	
3570	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(TFAc) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA		
3571	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , D—Lys(Nic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
3572	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , D—Lys(Pic) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(TFAc) ⁵ , D—Lys(TFAc) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA		
	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , 4-Cl—D—Phe ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , D—Nal ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , D—Lys(pGlu) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , D—Lys(OTac) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Ile ⁵ , D—Pal(Bzl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA		
3721	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(Pic) ⁵ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.3TFA	4/8 @ 1.0	
3722	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(3-Δ-Pro) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH-TFA	8/8 @ 5.0	
3723	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Ac) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0	
3740	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(pGlu) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1.0	
3741	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Ac) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	1/8 @ 1.0 6/8 @ 0.5	
3742	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Imdac) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1.0	

TABLE I-continued

LHRH Antagonists			
Compound	Sequence	AO activity (AOA)	Histamine release
10 3743	D—Pal ³ , D—Lys(Dodac) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	8/8 @ 1.0	
3753	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Ser ⁵ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 1.0	
15 3754	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(iPr) ⁵ , D—Lys(TFAc) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	5/8 @ 1.0	
3744	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , His ⁵ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 1.0	
20 3745	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Asn ⁵ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1.0	
3755	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , Lys(iPr) ⁵ , D—Lys(4HBC) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 1.0	
25 3756	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(iPr) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1.0	
3757	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , N—Me—Ala ⁵ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 1.0	
30 3758	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Hippic) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	5/8 @ 1.0	
3759	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(AcGly) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	5/8 @ 1.0	
35 3760	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Ppic) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	1/8 @ 1.0 7/8 @ 0.5	
3761	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Mus) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0	
40 3762	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Orotic) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1.0	
3763	Ac—Sar ¹ , 4-Cl—D—Phe ² , D—Nal ³ , D—Pal(Bzl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	4/8 @ 1.0	102 ¹ , 76 ^b
45 3769	Ac—Sar ¹ , 4-Cl—D—Phe ² , 1-1-Nal ³ , D—Pal(Bzl) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	6/8 @ 1.0	
3770	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Pal(CH ₂ COOH) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	6/8 @ 1.0 0.1 DMSO	
50 3771	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Ala) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0	
3772	Ac—Sar ¹ , 4-Cl—D—Phe ² , D-1-Nal ³ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	8/8 @ 1.0	
55 3773	Ac—Sar ¹ , 4-Cl—D—Phe ² , L—Nal ³ , D—Pal(iPr) ⁶ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.2TFA	7/8 @ 1.0	
3785	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Gulonyl) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0 0.1 DMSO	
60 3786	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Pal(N—O) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	4/8 @ 1.0	
3787	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Ppic) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0	
3800	Ac—D—Nal ¹ , 4-Cl—D—Phe ² , D—Pal ³ , D—Lys(Imdac) ⁵ , Lys(iPr) ⁸ , D—Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0	

TABLE I-continued

LHRH Antagonists		AO activity (AOA)	Hista- mine release
Com- pound	Sequence		
3801	Ac-D-Qal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Lys(Orn) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	8/8 @ 1.0	
3802	Ac-D-Qal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Lys(Orn) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	5/8 @ 1.0	
3803	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Lys(Dodac) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	2/8 @ 1.0	
3804	Ac-D-Pal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Pal(iPr) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	8/8 @ 1.0	
3827	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , N-Me-Tyr ⁵ , D-Asn ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	4/8 @ 1.0	
3828	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , N-Me-Tyr ⁵ , D-Lys(Orn) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	4/8 @ 1.0	42 ^a , 39 ^b
3829	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , N-Me-Tyr ⁵ , D-Lys(Asn) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	8/8 @ 1.0	
3852	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , Lys(iPr) ⁵ , D-His ⁶ , Trp ⁷ , Orn ⁸ , D-Ala ¹⁰ -LHRH.TFA	8/8 @ 5.0	
3853	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , His ⁵ , D-Arg ⁶ , Trp ⁷ , Orn ⁸ , D-Ala ¹⁰ -LHRH.TFA	0/8 @ 5.0	
3854	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , Arg ⁵ , D-His ⁶ , Trp ⁷ , Orn ⁸ , D-Ala ¹⁰ -LHRH.TFA	6/8 @ 5.0	
3855	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , Lys(iPr) ⁵ , D-Trp ⁶ , Trp ⁷ , Orn ⁸ , D-Ala ¹⁰ -LHRH.TFA	4/8 @ 1.0	
3851	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , 4-Cl-Phe ⁵ , D-Pal(iPr) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.0 6/8 @ 0.5	4.1 ^a , 5.4 ^b
3882	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal(N-O) ³ , D-Pal(iPr) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	6/8 @ 1.0	
3880	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Arg ⁵ , Met ⁸ , D-Ala ¹⁰ -LHRH.TFA	8/8 @ 1.0	
3878	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Arg ⁵ , Met(S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	2.8 @ 1.0 7/8 @ 0.5	
3881	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Met ⁶ , D-Ala ¹⁰ -LHRH.TFA	7/8 @ 1.0	
3879	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Met(S*Me) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.0 6/8 @ 0.5	
3926	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Arg ⁵ , Lys(COCH ₂ Br) ⁸ , D-Ala ¹⁰ -LHRH.TFA	6/8 @ 1.0	
3925	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Met(S*Me) ⁶ , Met(S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	5/8 @ 1.0	13 ^c , 5 ^d
3941	Met(S*Me) ⁸ -LHRH.TFA	8/8 @ 50.0	
3942	Lys(COCH ₂ Br) ⁸ -LHRH	8/8 @ 50.0	
3948	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Lys(COCH ₂ Br) ⁶ , D-Ala ¹⁰ -LHRH.TFA	low activity	
3949 ^a	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Lys(COCH ₂ CH ₂ N(Et) ₂) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	low activity	
3960	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Lys(2-pyrimidyl- thio)acetic) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.TFA	5/8 @ 1.00	
3961	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Met(S*CH ₂ C ₆ H ₅) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	4/8 @ 2.00 3/8 @ 1.00	

TABLE I-continued

LHRH Antagonists		AO activity (AOA)	Hista- mine release
Com- pound	Sequence		
3967	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Met(S*CH ₃) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	1/8 @ 0.5 7/8 @ 0.25	0.38 ^e , 0.15 ^f
3968 ^a	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Met(S*CH ₂ COPh) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	4/8 @ 1.00	
3969	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Dap(COCH ₂ S*Me) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	3/8 @ 1.00	
3982	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , His ⁵ -D-Pal(iPr) ⁶ , Lys(iPr) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	8/8 @ 1.00	53 ^c , 33 ^d
3983	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Arg ⁶ , Met(S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.00 8/8 @ 0.5 3/8 @ 1.00	5.35 ^h 1.32 ^h
3984	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Trp ³ , D-Met(S ³⁰ CH ₂ -CH=CH ₂) ⁶ , D-Ala ¹⁰ -LHRH.2TFA		
3985	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Arg ⁶ , Orn(COCH ₂ S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.00 8/8 @ 0.5	4.4 ^a , 3.86 ^b
3994	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Arg ⁶ , Orn(COCH ₂ SMe) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	6/8 @ 1.00	
3995	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Arg ⁶ , Met ⁸ , D-Ala ¹⁰ -LHRH.TFA	5/8 @ 1.00	
4014	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Lys(COCH ₂ S*Me) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.00	
4015	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Arg ⁶ , Lys(COCH ₂ S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	1/8 @ 1.00	
4016	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Met(S*Me) ⁶ , Met(S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	6/8 @ 1.00	
4013	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ , D-Orn(COCH ₂ S*Me) ⁶ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.00	
4023	Ac-D-Nal ¹ , 4-Cl-D-Phe ² , D-Pal ³ -D-Arg ⁶ , Dap(COCH ₂ S*Me) ⁸ , D-Ala ¹⁰ -LHRH.2TFA	0/8 @ 1.00	

^a Mass spectral analysis did not confirm the structure, Nal arg (reference) histamine release values: a = 0.11, b = 0.14, c = 0.28, d = 0.11, e = 0.1, f = 0.02, g = 0.1, h = 0.02

Sulfonium moieties confer high AOA on peptides when incorporated at position 6 (e.g., compound 3879) or position 8 (e.g., compound 3983). Compound 3925 (with two sulfonium moieties) showed low histamine release. Both alkyl and α -(sulfonium)carbonyl moieties (e.g., compound 4023) are effective. Preliminary experiments with LHRH agonists and antagonists suggest that compounds incorporating a bromoacetyl moiety are bound to the receptor and are not removed by repeated washing.

Certain peptides which have an N-alkyl pyridinium moiety at position 6 are unexpectedly active (e.g., compound 3851) in the AOA assay. Some have very little histamine-releasing activity (e.g., compound 3763) compared to the standard, Nal-Arg. These results are unexpected in light of the previously reported AOA activity and histamine-releasing qualities of N-methyl pyridinium compounds.

Dipolar moieties generally exhibited modest AOA. Compounds including Lys(Orn)⁶ exhibited favorable qualities; one (compound 3828) showed low histamine releasing activity, and compound 3507 showed high AOA.

25

Several peptides having acylated lysine at position 6 were tested, and showed good AO activity (e.g. compounds 3741 and 3760).

Compounds having a small polar moiety at position 6 exhibited favorable combinations of AOA and histamine-releasing activity. For example, compound 3827, which has D-Asn (a small, hydrophilic moiety) at position 6 showed moderate AO activity. Compounds 3341, 3342, and 3343 having D-Gln, D-Asn, and D-Thr, respectively, combined moderate AOA with very low histamine release. Compound 3361, which had the taurine amide of Glu at position 6, also showed very low histamine release. Compound 3369, which had D-Cit at position 6, also showed low histamine release.

All of the analogs listed in Table 1 can be synthesized by the solid phase method using an automated synthesizer (e.g., Beckman Model 990). The amino acid residues used can be purchased from commercial sources (e.g. Aldrich Chemical Co., Milwaukee, Wis.), or can be produced from commercially available starting materials according to known methods. For example, pyridinium-N-oxides can be produced by oxidation of the corresponding pyridine with, e.g., peroxyacids such as mCPBA (see, e.g., Example 3, *infra*). Pyridinium moieties, for example, N-benzyl pyridinium compounds, can be produced by N-alkylation of the corresponding pyridine, e.g., by heating in an inert solvent with benzyl bromide (see Examples 1 and 2, *infra*). Similarly, sulfonium and phosphonium salts can be produced by S- or P-alkylation of a sulfide or phosphine, respectively, with an alkylating agent such as, for example, methyl iodide. Amino acids which are not obtained commercially can be synthesized in a protected form for coupling, or, if appropriate, can be coupled to form a peptide and subsequently modified to the desired form.

EXAMPLE 1

Synthesis of Boc-D-Pal(Bzl) Hydrobromide Salt

Boc-D-Pal (1.36 g, 6.0 mmol) was suspended in 60 ml of acetonitrile. Benzyl bromide (about 50 mmol) was added and the mixture was warmed to 50° C. on a water bath. A clear solution resulted, and was stirred at room temperature for 16 hours. A white precipitate formed; TLC after 17 hours showed some starting remaining starting material; stirring continued for a total of 5 days, when the reaction was complete. The solvent was evaporated under reduced pressure, and the residue recrystallized from EtOH/ethyl acetate. Yield: 85%; m.p. 166°–170° C.

EXAMPLE 2

Synthesis of Boc-D-Pal(iPr)

Boc-D-Pal (4.0 g, 17.7 mmol) and Ag₂O (8.0 g, 34.4 mmol) in 22 ml water was stirred at room temperature for 4 hours. The reaction vessel was cooled to 0° C., and 2-iodopropane (20.4 g, 120 mmol) in 40 ml 2-propanol was added. After addition was complete, the mixture was allowed to warm to room temperature and stirred for 4 days. Additional Ag₂O (2 g) and 2-iodopropane (2 g) were added after 24 hours and again after 48 hours. The mixture was filtered, and the precipitate was washed with ethanol (2×15 ml). The filtrate was evaporated to yield 4.3 g of a yellow oil. Crystallization from ethanol/ethyl acetate gave light yellow crystals (3.0 g); Yield: 63%; m.p. 182°–185° C.

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EXAMPLE 3

Synthesis of Boc-D-Pal(N-O)

Boc-D-Pal (2.0 g, 7.5 mmole) was dissolved in 40 ml acetone and 2.48 g (16.5 mmol) of MCPBA (57–86%; purchased from Aldrich and used as received) in 80 ml acetone was added in one portion. The mixture was stirred at room temperature for 40 hours; a small amount of white precipitate formed as the reaction proceeded. The precipitate was filtered and the mother liquor evaporated to yield a white precipitate. The combined solids were washed with ether (to remove chlorobenzoic acid) and recrystallized from ethyl acetate/hexane. Yield: 1.7 g (80%); m.p. 155°–157° C.

EXAMPLE 4

A typical coupling cycle for peptide synthesis with Boc-amino acids on a peptide synthesizer (Beckman Model 990) was as follows:

Methylbenzylhydramine (MBHA) resin (1.18 g, 0.85 meq amino groups/g resin) was weighed into the reaction vessel and washed with two portions of chloroform (26 ml each). The resin was prewashed with 22% thioanisole (5 ml)/66% trifluoroacetic acid (TFA) in 14 ml dichloromethane (DCM) for 5 minutes, and then deprotected for 30 minutes with the same thioanisole/TFA mixture. The resin was washed with three portions of chloroform (20 ml each), two portions of 2-propanol (26 ml each) and two portions of DCM (26 ml each). The resin was neutralized with two portions of 12% diisopropylethylamine (DIPEA) (26 ml each), and then washed with four portions of DCM (26 ml each), followed by two portions of 1:1 DCM:dimethylformamide (DMF) (26 ml each). A solution of a Boc-protected amino acid (2.5 mole equivalents) and HOBt (2.5 mole equivalents) was introduced as a solution in 10 ml DMF, and DCC was added (256 mg in 6 DMF). Coupling was allowed to proceed for three hours, or overnight. Hindered residues (e.g., backbone N-methyl amino acids) required longer coupling times. The resin was washed with two 26 ml portions of DMF, followed by two 26 ml portions of 2-propanol and then two 26 ml portions of DCM. Completion of coupling was assessed by Kaiser's test (ninhydrin test). If coupling is not complete, a double coupling was performed (i.e., the resin was neutralized as above and the coupling step repeated). When complete coupling is achieved, the cycle was repeated with the next amino acid.

Upon completion of the synthesis, the peptide was cleaved from the resin by treatment with liquid hydrofluoric acid (HF) for 45 minutes at 0° C. The HF was evaporated and the peptide treated with aqueous acetic acid and lyophilized. The crude peptide was then purified by high performance liquid chromatography (HPLC) on a C₁₈ column, eluting with a mixture of acetonitrile and 0.1% TFA in water. Purified fractions (homogeneous by UV and TLC analysis) were combined and lyophilized. Analytical HPLC was used to determine the purity of the final product; all peptides synthesized were at least 98% pure.

The contents of all references cited throughout this patent application are hereby incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 6

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

G	l	u		H	i	s		T	r	p		S	e	r		T	y	r		G	l	y		L	e	u		A	r	g		P	r	o		G	l	y
1																5																						10

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 1

(D) OTHER INFORMATION: /note= Xaa is pyroglutamyl or acetylsarcosine

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 3

(D) OTHER INFORMATION: /note= Xaa is Trp or 3-(2- naphthyl)alaninyl

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 5

(D) OTHER INFORMATION: /note= Xaa is N-methyl-Ala, Tyr, N-methyl- Tyr, Ser, N-ε-2-propyl-lysiny, (4 ' - c h l o r o p h e n y l)alaninyl, His, Asn, Met, Ala, Arg or Ile

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 6

(D) OTHER INFORMATION: /note= Xaa is an amino acid having a side chain comprising a dipolar moiety

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 7

(D) OTHER INFORMATION: /note= Xaa is Leu or Trp

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 8

(D) OTHER INFORMATION: /note= Xaa is N-ε-2-propyl-lysiny, Gln, Met or Arg

(i x) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 10

(D) OTHER INFORMATION: /note= Xaa is Gly-NH2

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

X	a	a		H	i	s		X	a	a		S	e	r		X	a	a		X	a	a		X	a	a		X	a	a		P	r	o		X	a	a
1																5																						10

(2) INFORMATION FOR SEQ ID NO:3:

```

( i ) SEQUENCE CHARACTERISTICS:
      ( A ) LENGTH: 10 amino acids
      ( B ) TYPE: amino acid
      ( D ) TOPOLOGY: linear

( i i ) MOLECULE TYPE: peptide

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 1
      ( D ) OTHER INFORMATION: /note= Xaa is pyroglutamyl or
                                acetylsarcosine

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 3
      ( D ) OTHER INFORMATION: /note= Xaa is Trp or
                                3-(2- naphthyl)alaninyl

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 5
      ( D ) OTHER INFORMATION: /note= Xaa is N-methyl-Ala, Tyr,
                                N-methyl- Tyr, Ser, N-e-2-propyl-lysinyI,
                                ( 4 ' - c h l o r o p h e n y l )alaninyl, His, Asn, Met, Ala, Arg or Ile

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 6
      ( D ) OTHER INFORMATION: /note= Xaa is an amino acid having a
                                side chain comprising a cationic moiety

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 7
      ( D ) OTHER INFORMATION: /note= Xaa is Leu or Trp

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 8
      ( D ) OTHER INFORMATION: /note= Xaa is N-e-2-propyl-lysinyI,
                                Gln, Met or Arg

( i x ) FEATURE:
      ( A ) NAME/KEY: Modified-site
      ( B ) LOCATION: 10
      ( D ) OTHER INFORMATION: /note= Xaa is Gly-NH2

( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:3:
Xaa A His Xaa S cr Xaa Xaa Xaa Xaa P ro Xaa
1 1 1 1 1 1 1 1 1 1 1 1
5
1 0

```

(2) INFORMATION FOR SEQ ID NO:4:

- ```
(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i x) FEATURE:
 (A) NAME/KEY: Modified-site
 (B) LOCATION: 1
 (D) OTHER INFORMATION: /note= Xaa is pyroglutamyl or
 acetylsarcosine

(i x) FEATURE:
 (A) NAME/KEY: Modified-site
 (B) LOCATION: 3
 (D) OTHER INFORMATION: /note= Xaa is Trp or
 3-(2- naphthyl)alaninyl

(i x) FEATURE:
 (A) NAME/KEY: Modified-site
 (B) LOCATION: 5
 (D) OTHER INFORMATION: /note= Xaa is N-methyl-Ala, Tyr,
```

-continued

N-methyl- Tyr, Ser, N-ε-2-propyl-lysinyI,  
( 4 ' - c h l o r o p h e n y l )alaninyI, His, Asn, Met, Ala, Arg or Ile

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 6
- ( D ) OTHER INFORMATION: /note= Xaa is an amino acid having a  
side chain comprising a receptor-modifying moiety

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 7
- ( D ) OTHER INFORMATION: /note= Xaa is Leu or Trp

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 8
- ( D ) OTHER INFORMATION: /note= Xaa is N-ε-2-propyl-lysinyI,  
Gln, Met or Arg

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 10
- ( D ) OTHER INFORMATION: /note= Xaa is Gly-NH2

## ( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:4:

|       |       |       |       |       |       |       |       |       |       |
|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| X a a | H i s | X a a | S e r | X a a | X a a | X a a | X a a | P r o | X a a |
| 1     |       |       |       | 5     |       |       |       |       | 10    |

## ( 2 ) INFORMATION FOR SEQ ID NO:5:

## ( i ) SEQUENCE CHARACTERISTICS:

- ( A ) LENGTH: 10 amino acids
- ( B ) TYPE: amino acid
- ( D ) TOPOLOGY: linear

## ( i i ) MOLECULE TYPE: peptide

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 1
- ( D ) OTHER INFORMATION: /note= Xaa is pyroglutamyl or  
acetylsarcosine

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 3
- ( D ) OTHER INFORMATION: /note= Xaa is Trp or  
3-(2- naphthyl)alaninyI

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 5
- ( D ) OTHER INFORMATION: /note= Xaa is N-methyl-Ala, Tyr,  
N-methyl- Tyr, Ser, N-ε-2-propyl-lysinyI,  
( 4 ' - c h l o r o p h e n y l )alaninyI, His, Asn, Met, Ala, Arg or Ile

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 6
- ( D ) OTHER INFORMATION: /note= Xaa is an amino acid having a  
side chain comprising an N-acyl hydrophilic moiety

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 7
- ( D ) OTHER INFORMATION: /note= Xaa is Leu or Trp

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 8
- ( D ) OTHER INFORMATION: /note= Xaa is N-ε-2-propyl-lysinyI,  
Gln, Met or Arg

## ( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 10
- ( D ) OTHER INFORMATION: /note= Xaa is Gly-NH2

-continued

( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:5:

X a a H i s X a a S e r X a a X a a X a a X a a P r o X a a  
 1 5 10

( 2 ) INFORMATION FOR SEQ ID NO:6:

( i ) SEQUENCE CHARACTERISTICS:

- ( A ) LENGTH: 10 amino acids
- ( B ) TYPE: amino acid
- ( D ) TOPOLOGY: linear

( i i ) MOLECULE TYPE: peptide

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 1
- ( D ) OTHER INFORMATION: /note= Xaa is pyroglutamyl or acetylsarcosine

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 3
- ( D ) OTHER INFORMATION: /note= Xaa is Trp or 3-(2- naphthyl)alaninyl

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 5
- ( D ) OTHER INFORMATION: /note= Xaa is N-methyl-Ala, Tyr, N-methyl- Tyr, Ser, N-c-2-propyl-lysiny, ( 4 ' - c h l o r o p h e n y l )alaninyl, His, Asn, Met, Ala, Arg or Ile

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 6
- ( D ) OTHER INFORMATION: /note= Xaa is an amino acid having a side chain comprising a small polar moiety

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 7
- ( D ) OTHER INFORMATION: /note= Xaa is Leu or Trp

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 8
- ( D ) OTHER INFORMATION: /note= Xaa is N-c-2-propyl-lysiny, Gln, Met or Arg

( i x ) FEATURE:

- ( A ) NAME/KEY: Modified-site
- ( B ) LOCATION: 10
- ( D ) OTHER INFORMATION: /note= Xaa is Gly-NH<sub>2</sub>

( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:6:

X a a H i s X a a S e r X a a X a a X a a P r o X a a  
 1 5 10

What is claimed is:

1. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal;  
 B is His or 4-Cl-D-Phe;  
 C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;  
 D is Ser;  
 E is N-Mc-Ala, Tyr, N-Mc-Tyr, Ser, Lys(iPr), 4-Cl-Phe,  
 His, Asn, Met, Ala, Arg or Ile;  
 F is D-Asn or D-Gln;  
 G is Leu or Trp;

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H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-NH<sub>2</sub> or D-Ala-NH<sub>2</sub>;  
 or a pharmaceutically acceptable salt thereof.

2. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

60

wherein

A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal;  
 B is His or 4-Cl-D-Phe;  
 C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;  
 D is Ser;  
 E is N-Mc-Ala, Tyr, N-Mc-Tyr, Ser, Lys(iPr), 4-Cl-Phe,  
 His, Asn, Met, Ala, Arg or Ile;

65



## 35

F is D-Asn;  
G is Leu or Trp;  
H is Lys(iPr), Gln, Met, or Arg;  
I is Pro; and  
J is Gly-NH<sub>2</sub> or D-Ala-NH<sub>2</sub>;  
or a pharmaceutically acceptable salt thereof.  
3. A peptide compound comprising a structure:  
Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-N-Me-Tyr-D-Asn-Leu-  
Lys(iPr)-Pro-D-Ala-NH<sub>2</sub>;

## 36

or a pharmaceutically acceptable salt thereof.  
4. A peptide compound comprising a structure:  
Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Asn-Leu-Lys  
(iPr)-Pro-D-Ala-NH<sub>2</sub>;  
5 or a pharmaceutically acceptable salt thereof.  
5. A pharmaceutical composition comprising the peptide  
compound of any one of claims 1, 2, 3 or 4, and a  
pharmaceutically acceptable carrier.

\* \* \* \* \*



EXHIBIT B  
UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

COPY

959

M75N4

LAHIVE & COCKFIELD  
28 STATE STREET  
BOSTON MA 02109

## MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

| ITEM<br>NBR | PATENT<br>NUMBER | FEE<br>CDE | FEE<br>AMT | SUR<br>CHARGE | SERIAL<br>NUMBER | PATENT<br>DATE | FILE<br>DATE | PAY SML<br>YR ENT | STAT |
|-------------|------------------|------------|------------|---------------|------------------|----------------|--------------|-------------------|------|
| 1           | 5,843,901        | 183        | 880        |               | 08/480,494       | 12/01/98       | 06/07/95     | 04 NO             | PAID |

|                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------|
| RECEIVED<br>LAHIVE & COCKFIELD<br>DOCKET DEPT.<br><br>JUN 28 2002<br><br>RETRIEVED: <u>    </u><br>FORWARDED: <u>    </u> |
|---------------------------------------------------------------------------------------------------------------------------|

ITM  
NBR

1

ATTY DKT  
NUMBER

PPI-007

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:  
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231



DEPARTMENT OF HEALTH & HUMAN SERVICES

EXHIBIT C  
Public Health Service

Food and Drug Administration  
Rockville MD 20857

IND 51,710

OCT 22 1996

Pharmaceutical Peptides, Inc.  
Attention: Marc B. Garnick, M.D.  
1 Hampshire Street  
Cambridge, Massachusetts 02139-1572

Dear Dr. Garnick:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 51,710  
Sponsor: Pharmaceutical Peptides, Inc  
Name of Drug: PPI-149 (treatment of prostate cancer)  
Date of Submission: October 18, 1996  
Date of Receipt: October 18, 1996

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of information; reporting any unexpected fatal or life-threatening experience to FDA by telephone no later than three working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

IND 51,710

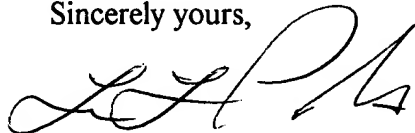
Page 2

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Attention: Document Control Room 17B-20  
5600 Fishers Lane  
Rockville, Maryland 20857

Should you have any questions concerning this submission, please contact Lana L. Pauls, M.P.H. at 301-827-4260.

Sincerely yours,

A handwritten signature in cursive script, appearing to read 'L.L. Pauls', written in dark ink.

Lana L. Pauls, M.P.H.  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation II  
Center of Drug Evaluation and Research



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-320

Praecis Pharmaceuticals  
Attention: JD Bernardy, J.D.  
Vice President, Regulatory Affairs  
One Hampshire Street  
Cambridge, MA 02139

Dear Mr. Bernardy:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Plenaxis™ Depot (abarelix for depot suspension)

Review Priority Classification: Priority (P)

Date of Application: December 11, 2000

Date of Receipt: December 12, 2000

Our Reference Number: NDA 21-320

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 10, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 12, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application.

In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

/s/

-----  
Terri F. Rumble

1/8/01 04:17:36 PM



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

---

Food and Drug Administration  
Rockville, MD 20857

NDA 21-320

Praecis Pharmaceuticals, Inc.  
Attention: JD Bernardy, J.D.  
Vice President, Regulatory Affairs and Quality Assurance  
830 Winter Street  
Waltham, MA 02451-1420

Dear Mr. Bernardy:

We acknowledge receipt on February 27, 2003 of your February 25, 2003 resubmission to your new drug application for Plenaxis™ (abarelix for injectable suspension).

We consider this a complete, class 2 response to our June 11, 2002 action letter. Therefore, the user fee goal date is August 27, 2003.

If you have any question, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph.  
Chief, Project Management Staff  
Division of Division of Reproductive and  
Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research



-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Margaret Kober  
3/18/03 11:20:28 AM  
Chief, Project Management Staff



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-320

Praecis Pharmaceuticals, Incorporated  
Attention: J.D. Bernardy, J.D.  
Vice President, Regulatory Affairs & Quality Assurance  
830 Winter Street  
Waltham, MA 02451-1420

Dear Mr. Bernardy:

Please refer to your new drug application (NDA) dated December 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plenaxis™ (abarelix for injectable suspension, 100mg).

We acknowledge receipt of your submissions dated January 5; March 13, 14, 15, 26, 27, 29, and 30; April 6, 9, 10, 13, 17, 19, 26, and 27(2); May 4, 7, 10, 22, 24, 25(2), and 29; June 14 and 15; and July 26, 2001; February 25, March 19 and 20; April 25(2); May 8 and 16(2); June 3, 5, 17, 19, 25, 27, and 30; July 9, 11, 14, 16, 17, 18, 29, and 31; August 8; September 10, 12, 17, 24, and 29; October 3, 14, 20, 24, and 30(2); and November 3, 4, 7, 11, 13, 16, 17, 18(2), 19, 21(2), and 24, 2003.

The February 25, 2003 submission constituted a complete response to our Not Approvable letter of June 11, 2001. The original submission was not approved because of the risk of serious allergic reactions, including anaphylaxis with hypotension and syncope, and because the risk of loss of efficacy over time. For your then proposed target population of men with local, regional, or advanced carcinoma of the prostate where androgen suppression is appropriate, the Agency determined that risks of Plenaxis™ exceeded its benefits.

This resubmission of the application provides for the use of Plenaxis™ (abarelix for injectable suspension, 100mg) for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

The resubmitted application, considered for approval under 21 CFR Part 314, Subpart H at your request, narrows the originally proposed indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks, but in whom the drug can be safely used only if distribution and/or use is restricted. The application provides for a risk management program that will help ensure the safe use of Plenaxis™ in the approved indicated population.

We completed our review of this application, as amended, and have concluded that adequate information has been presented to approve this application for Plenaxis™ (abarelix for injectable suspension, 100mg) under 21 CFR Part 314 Subpart H for the proposed indication in your resubmission. You have indicated your agreement with approval with restrictions to ensure safe use. Accordingly, this application is approved under 21 CFR Part 314, Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be accordance with applicable provisions of the Act and FDA regulations, including the specific restrictions on distribution and use described below.

Plenaxis™ Risk Management Program

We remind you that your Plenaxis™ Risk Management Program is an important part of postmarketing risk management for Plenaxis™, and must include each of the following components in order to ensure distribution only to physicians with the training and experience necessary to assure safe use of the drug, and to ensure use of Plenaxis™ only in patients for whom the drug is indicated, as set forth in the INDICATIONS AND USAGE section of the FDA-approved labeling:

1. Enrollment of qualified physicians in a physician prescribing program that ensures that Plenaxis™ is distributed only to these enrolled physicians and that the use of Plenaxis™ is in the approved indicated population.
2. Implementation of a program to educate physicians, hospital pharmacists, patients, and distributors about the risks and benefits of Plenaxis™ and responsibilities of being part of the prescribing program.
3. Implementation of a reporting and collection system for serious adverse events associated with the use of Plenaxis™ that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
4. Implementation of a plan to evaluate the effectiveness of the Plenaxis™ Risk Management Program.

The Plenaxis™ Risk Management Program, as described in the attached documents, adequately addresses each of these requirements. Any change to the program must be discussed with the FDA prior to its institution and is subject to FDA approval. We expect your continued cooperation to resolve any problems regarding the Plenaxis™ Risk Management Program that may be identified following approval of your application.

Within the first year of the initiation of the Risk Management Program, and annually thereafter, you must provide the FDA with a report under 21 CFR 314.80(b)(2) that describes how each element of the program has been implemented, provides implementation data, and evaluates the success of the program using, among other available data, the studies, audits, and evaluations described in the Plenaxis™ Risk Management Program and postmarketing commitments #1, 2, 3, and 4 below.

We remind you of your specific reporting obligations regarding adverse events of patients who have received Plenaxis™. As set forth in the attached document, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), you will initiate a 15-day report for each of the following:

1. All spontaneous reports of anaphylaxis, anaphylactic reaction, anaphylactoid reaction, anaphylactic shock, angioedema of the throat, angioedema of the tongue, laryngeal obstruction,

- laryngeal angioedema, upper respiratory tract obstruction, systemic allergic reaction, immediate hypersensitivity reaction, acute bronchospasm, or wheezing.
2. All spontaneous reports of syncope, near-syncope, loss of consciousness, shock, or hypotension.
  3. All spontaneous reports involving treatment with epinephrine, parenteral antihistamine, inhaled bronchodilators, parenteral corticosteroids, intubation, tracheostomy, or cricothyroidotomy.
  4. All spontaneous reports of hospitalizations or emergency room visits for urticaria or angioedema.
  5. All spontaneous reports of death, regardless of causality.

Postmarketing Commitments

You have committed to conduct the postmarketing studies, specified in your submission dated November 21, 2003 that are listed below:

1. Conduct studies of a random sample of all enrolled prescribers as part of your risk management evaluation program to survey physician knowledge and understanding of risks and benefits of Plenaxis<sup>™</sup> and responsibilities under the prescribing program. Praecis Pharmaceuticals Incorporated and FDA will review the study findings and agree to educational and/or other activities that may be needed to address observations.  

|                          |                       |
|--------------------------|-----------------------|
| Protocol Submission:     | by February 27, 2004  |
| Study Start:             | by September 30, 2004 |
| Final Report Submission: | by September 30, 2008 |
2. Conduct a study ancillary to the 2000 patient "Plenaxis<sup>™</sup> Experience Study" (see commitment #5) as part of the risk management evaluation program to evaluate use of Plenaxis<sup>™</sup> by physicians in the approved, indicated population. Provide an assessment of the frequency of signed Patient Information signature pages filed in the patient's medical record, frequency of serum testosterone testing, and other physician responsibilities accepted as part of the Plenaxis<sup>™</sup> Prescribing Program. Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.  

|                          |                       |
|--------------------------|-----------------------|
| Protocol Submission:     | by January 30, 2004   |
| Study Start:             | by June 30, 2004      |
| Final Report Submission: | by September 30, 2008 |
3. Conduct a study involving use of Plenaxis<sup>™</sup> through a case claims survey performed by a managed care organization. The survey will provide an assessment of whether Plenaxis<sup>™</sup> is being used in the indicated population (e.g., review of formulary restrictions and patient information concerning age, sex, and diagnosis). Praecis Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.  

|                          |                       |
|--------------------------|-----------------------|
| Protocol Submission:     | by February 27, 2004  |
| Study Start:             | by September 30, 2004 |
| Final Report Submission: | by September 30, 2008 |
4. Conduct a study as part of the risk management evaluation program to evaluate adherence to attested responsibilities of the prescribing program for hospital pharmacies. Praecis

Pharmaceuticals Incorporated and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

Protocol Submission: by February 27, 2004  
Study Start: by September 30, 2004  
Final Report Submission: by September 30, 2008

5. Conduct a study of 2,000 patients to estimate the incidence of immediate-onset systemic allergic reactions (anaphylaxis, hypotension and/or syncope) in the indicated population receiving Plenaxis<sup>™</sup> and to determine whether the hazard rate changes over time.

Protocol Submission: by January 30, 2004  
Study Start: by June 30, 2004  
Final Report Submission: by September 30, 2008

6. Conduct a clinical study to characterize Plenaxis<sup>™</sup>-induced immediate-onset system allergic reactions by evaluating skin test reactivity to Plenaxis<sup>™</sup> and determining anti-abarelix IgG and IgE antibody levels for patients experiencing immediate-onset systemic allergic reactions.

Protocol Submission: by January 30, 2004  
Study Start: by June 30, 2004  
Final Report Submission: by September 30, 2008

7. Conduct a clinical study to assess the effectiveness of pre-treatment with oral antihistamine with or without oral steroids for patients who experience Plenaxis<sup>™</sup>-induced urticaria and/or pruritis within 2 hours of drug administration and continue Plenaxis<sup>™</sup> therapy.

Protocol Submission: by January 30, 2004  
Study Start: by June 30, 2004  
Final Report Submission: by September 30, 2008

Submit your clinical study protocols to your IND for this product. We encourage you to submit your study protocols to the Division of Reproductive and Urologic Drug Products for review and comment prior to the initiation of your postmarketing studies. Submit nonclinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **“Postmarketing Study Protocol”, “Postmarketing Study Final Report”, or “Postmarketing Study Correspondence.”**

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text submitted on November 24, 2003, for the Product Information insert, the Patient Information form, and the Physician Attestation form; and identical to the immediate container and carton labels submitted on November 24, 2003. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15

of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-320.**" Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.550, after the initial 120 day period following approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and labeling directly to:

Division of Drug Marketing, Advertising,  
and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Florence Houn, MD MPH  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosures

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Florence Houn

11/25/03 02:59:04 PM

## PATENT ASSIGNMENT

THIS PATENT ASSIGNMENT (the "Assignment"), made as of the 30th day of June, 1997, by and between Indiana University Foundation, a nonprofit corporation organized under the laws of the State of Indiana, ("Assignor"), and the Advanced Research & Technology Institute, an Indiana nonprofit entity incorporated in 1996 to assist Indiana University ("Assignee").

## WITNESSETH

WHEREAS, Assignor has previously been assigned right, title, and interest in property listed on Schedule A attached hereto by the Inventor of said property; and

WHEREAS, Assignee is desirous of acquiring Assignor's interest in the same;

NOW, THEREFORE, in consideration of the premises set forth herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Assignor agrees as follows:

**1. Assignment of Patents.** Assignor hereby grants, conveys, and assigns to Assignee, all of Assignor's right, title, and interest in and to all of its now owned or existing:

1. U.S. and foreign patents and patent applications including, without limitation, the inventions and improvements described and claimed therein, as listed on Schedule A attached hereto (hereinafter called "Patents");
2. The reissues, divisions, continuations, renewals, extensions, continuations-in-part, and improvements thereof;
3. All income, royalties, damages, and payments now and hereafter due and/or payable under and with respect thereto, including, without limitation, damages and payments for past or future infringements thereof; and
4. The right to sue and recover for past, present, and future infringements thereof.



2. **Covenants and Warranties.** Assignor represents, warrants, and covenants that:

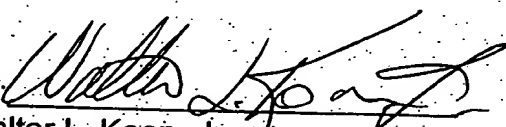
1. The Patents are subsisting, have not been adjudged invalid or unenforceable in whole or in part, and are not currently being challenged in any way;
2. None of the Patents has lapsed or expired;
3. No claim has been made that the use of any of the Patents constitutes an infringement of any senior or dominant U.S. patent or other intellectual property right; and
4. Assignor has the full right to convey the right, title and interest herein assigned.


3. **Binding effect; Benefits.** This Assignment shall be binding upon Assignor and its respective successors and assigns and shall inure to the benefit of Assignee, its nominees, successors, and assigns.

4. **Authorization and Request.** Assignor authorizes and requests the Commissioner of Patents and Trademarks to issue in the name of the Assignee any and all patents of the United States to issue from pending patent applications, or reissues, divisions, continuations, renewals, extensions, continuations-in-part or improvements resulting from Patents.

WITNESS the due execution hereof as of the date first above written.

Indiana University Foundation

By   
Walter L. Koon, Jr.  
Senior Vice President, Investments

Attest:   
Carol S. Gross  
Corporate Secretary

Accepted:

Advanced Research & Technology Institute

By: Douglas M. Wilson  
Douglas Wilson  
President

cc: Julie M. Watson  
Vice President  
Advanced Research and Technology Institute

g:\heather\patent.doc

TABLE 1 - ISSUED U.S. PATENTS

| PATENT NUMBER | ISSUE DATE    | INVENTORS       |
|---------------|---------------|-----------------|
| 4,851,385     | July 25, 1989 | Roger W. Roeske |

TABLE 1 - ISSUED U.S. PATENTS

| PATENT NUMBER | ISSUE DATE        | INVENTORS       |
|---------------|-------------------|-----------------|
| 4,547,370     | November 29, 1983 | Roger W. Roeske |

TABLE 2 - PENDING U.S. PATENTS

| SERIAL NO. | FILING DATE | INVENTORS | TITLE |
|------------|-------------|-----------|-------|
|------------|-------------|-----------|-------|

|            |              |              |  |
|------------|--------------|--------------|--|
| 08/480,494 | June 7, 1995 | Roger Roeske |  |
|------------|--------------|--------------|--|

ISSUED AND PENDING FOREIGN PATENTS

| COUNTRY | PATENT<br>NUMBER | ISSUE<br>DATE | SERIAL<br>NUMBER | FILING<br>DATE | INVENTORS | TITLE |
|---------|------------------|---------------|------------------|----------------|-----------|-------|
|---------|------------------|---------------|------------------|----------------|-----------|-------|

|     |  |  |                |              |              |  |
|-----|--|--|----------------|--------------|--------------|--|
| PCT |  |  | PCT/US96/09852 | June 7, 1996 | Roger Roeske |  |
|-----|--|--|----------------|--------------|--------------|--|

LAHIVE  
&  
COCKFIELD  
L L P

COUNSELLORS AT LAW  
28 STATE STREET  
BOSTON, MASSACHUSETTS 02109-1784  
TELEPHONE (617) 227-7400  
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lc@lahcoc.com

JOHN A. LAHIVE, JR. (1928-1997)  
W. HUGO LIEPMANN  
JAMES E. COCKFIELD  
THOMAS V. SMURZYNSKI  
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THOMAS J. ENGELLENER  
GIULIO A. DeCONTI, JR.  
ANN LAMPORT HAMMITTE  
ELIZABETH A. HANLEY  
AMY BAKER MANDRAGOURAS  
JOHN V. BIANCO  
ANTHONY A. LAURENTANO  
JANE E. REMILLARD  
CHARLES ERIC SCHULMAN  
FAUSTINO A. LICAUCO

SCOTT D. ROTHENBERGER, Ph.D.  
DAVID A. LANE, JR.  
LINDA M. CHINN  
JEANNE M. DIGIORGIO  
DEBRA J. MILASINCIC, Ph.D.  
LAURANNE S. BUTLER  
NICHOLAS P. TRIANO III

OF COUNSEL  
JEREMIAH LYNCH  
LAWRENCE E. MONKS  
WILLIAM A. SCOFIELD, JR.  
KEVIN J. CANNING  
PETER C. LAURO \*

\*Admitted in NY only

PATENT  
CATHERINE  
MEGAN

TECHNICAL  
DIANA M. CO  
JASBIR K. SA  
MARIA C. LAC  
REZA MOLLAA  
MONICA PALAC  
CYNTHIA M. SORO

October 21, 1998

**VIA DHL COURIER**

J. Gerald Holdcroft  
Graham Watt & Co.  
Riverhead Sevenoaks  
Kent TN13 2BN  
ENGLAND

Re: European Application No. 96 91 9311.9  
Based on International Application No. PCT/US96/09852  
Applicant: INDIANA UNIVERSITY FOUNDATION  
Title: LHRH ANTAGONIST PEPTIDES  
Your Reference: No. 12779  
Our Reference: PPI-007CPEP

Dear Gerry:

Enclosed please find an executed Assignment for the above-identified European application transferring rights from Indiana University Foundation to Advanced Research Technology Institute.

If you have any questions, please do not hesitate to contact us.

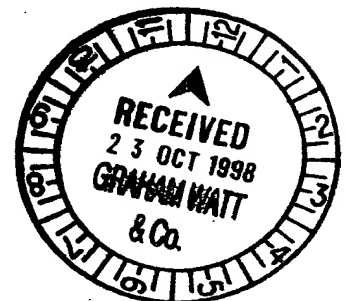
Very truly yours,

*Catherine*

Catherine J. Kara, Ph.D.

CJK/bsc  
Enclosure

cc: Dr. William Kubasek (w/ enclosure)  
Anthony T. Armstrong, Esq. (w/enclosure)  
Maria C. Laccotripe, Ph.D. (w/o enclosure)  
Giulio A. DeConti, Jr., Esq. (w/o enclosure)



THIS ASSIGNMENT is made the 30th day of June, One thousand nine hundred and ninety seven BETWEEN Indiana University Foundation (hereinafter called "the Assignors" which expression shall where the context so admits include their successors and assigns) of the one part and Advanced Research and Technology Institute, a nonprofit Corporation duly organised under the laws of the State of Indiana, United States of America of 501 North Morton, Suite 111, Bloomington, Indiana 47404, United States of America (hereinafter called "the Assignees" which expression shall where the context so admits include their successors and assigns) of the other part.

WHEREAS:

- a) The Assignors are the applicants in the European Patent Application identified in the Schedule hereto (hereinafter called "the said Application").
- b) For the consideration hereinafter appearing, the Assignors have agreed to assign to the Assignees and the Assignees have agreed to accept, the entire right title and interest in and to the said Application, the Invention thereof (hereinafter called "the said Invention") and any European patent granted on the said Application in respect of the designated contracting States as set out in the Schedule hereto, and the full right to apply for and obtain patent or other similar forms of protection in respect of the said Invention in any part of the world.

WITNESSETH:

1. In pursuance of the said agreement and in consideration of the sum of one hundred pounds sterling (£100.00) now paid by the Assignees to the Assignors (the receipt whereof the Assignors hereby acknowledge) the Assignors hereby assign with full title guarantee (and the Assignees hereby accept) all the right title



and interest of the Assignors in and to the said Invention and the said Application TOGETHER WITH all privileges benefits advantages and rights of actions appertaining thereto belonging or accrued to the effect that the said Application and any European patent granted on the said Application shall be registered in the name of and shall vest in the Assignees in respect of all the designated States as aforesaid including the right to sue for and benefit from any damages and other compensation awarded in respect of any infringements which may have occurred subsequent to the publication of the said Application and including also the full right to apply for obtain and hold patent or similar forms of protection in respect of the said Invention in any part of the world TO HOLD the same unto the Assignees their successors and assigns absolutely.

2. At the request and cost of the Assignees the Assignors shall assist in the prosecution of the said Application to grant and will execute all such documents and do all such acts as may be necessary or proper for procuring grant of any European patent on the said Application to the Assignees in respect of each of the designated States as aforesaid.

3. At the request and cost of the Assignees the Assignors shall execute all such documents and do all such acts as may be necessary or proper for procuring the grant of patent or similar forms of protection in respect of the said Invention in any part of the world.

4. In respect of any action or other proceedings for infringement the Assignors at the expense of the Assignees will render all available assistance of which they are capable in support thereof.

5. It is hereby certified that the transaction hereby effected

does not form part of a larger transaction or a series of transactions in respect of which the amount or value or the aggregate amount or value exceeds sixty thousand pounds sterling (£60,000.00).

SCHEDULE

Application No.

96 91 9311.9

Contracting States

AT, BE, CH, DE, DK, ES,  
FI, FR, GB, GR, IE, IT,  
LI, LU, MC, NL, PT, SE.

IN WITNESS whereof the parties have executed these presents with effect from the day and year above written.

Indiana University Foundation

By: Walter L. Koon, Jr. X

I hereby certify that the said Walter L. Koon, Jr. X Sr. VP Investments who executed this document in my presence is duly authorised to sign on behalf of Indiana University Foundation

Tamera B. Hyland  
Notary Public

Tamera B. Hyland, commission expires: August 15, 1999

Residing in Monroe County

Advanced Research Technology Institute

By: Douglas M. Wilson X

I hereby certify that the said Douglas M. Wilson X, President who executed this document in my presence is duly authorised to sign on behalf of Advanced Research Technology Institute

Cherie E. O'Brien  
Notary Public.

Residing in Monroe County, Indiana.

My commission expires February 19, 2008.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EL982739183US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: January 9, 2004

Signature: 

Jane E. Remillard

Docket No.: PPI-007  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of: Roger W. Roeske

U.S. Patent No: 5,843,901

Issued: December 1, 1998

For: LHRH ANTAGONIST PEPTIDES

MailStop Patent Ext.  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**POWER OF ATTORNEY**

Dear Sir:

Advanced Research and Technology Institute, the Assignee of the entire right, title and interest in the above-identified patent, hereby appoints the below listed attorneys with full power to prosecute the above-referenced patent and to transact all business in the Patent Office connected therewith.

|                        |                 |                                |                           |
|------------------------|-----------------|--------------------------------|---------------------------|
| James E. Cockfield     | Reg. No. 19,162 | Maria C. Laccotripe Zacharakis | Limited Recognition       |
| Thomas V. Smurzynski   | Reg. No. 24,798 |                                | Under 37 C.F.R. § 10.9(b) |
| Ralph A. Loren         | Reg. No. 29,325 | Debra J. Milasincic            | Reg. No. 46,931           |
| Giulio A. DeConti, Jr. | Reg. No. 31,503 | David R. Burns                 | Reg. No. 46,590           |
| Elizabeth A. Hanley    | Reg. No. 33,505 | Sean D. Detweiler              | Reg. No. 42,482           |
| Amy E. Mandragouras    | Reg. No. 36,207 | Cynthia L. Kanik               | Reg. No. 37,320           |
| Anthony A. Laurentano  | Reg. No. 38,220 | Theodore R. West               | Reg. No. 47,202           |
| Kevin J. Canning       | Reg. No. 35,470 | Hathaway P. Russell            | Reg. No. 46,488           |
| Jane E. Remillard      | Reg. No. 38,872 | John S. Curran                 | Reg. No. 50,445           |
| DeAnn F. Smith         | Reg. No. 36,683 | Lisa M. DiRocco                | Reg. No. 51,619           |
| Jeanne M. DiGiorgio    | Reg. No. 41,710 | Danielle L. Herritt            | Reg. No. 43,670           |
| Megan E. Williams      | Reg. No. 43,270 | Merideth C. Arnold             | Reg. No. 52,568           |
| Jeremiah Lynch         | Reg. No. 17,425 | Peter W. Dini                  | Reg. No. 52,821           |
| David J. Ridders       | Reg. No. 43,882 | Cynthia M. Soroos              | Reg. No. 53,623           |
|                        |                 | Jonathan M. Sparks             | Reg. No. 53,624           |
|                        |                 | Andrina M. Zink                | Reg. No. 54,539           |
|                        |                 | John D. Lanza                  | Reg. No. 40,060           |

of LAHIVE & COCKFIELD, LLP, 28 State Street, Boston, Massachusetts 02109, United States of America.

Please continue to send all correspondence relating to the above patent application to:

Giulio A. DeConti, Jr., Esq.  
LAHIVE & COCKFIELD, LLP  
28 State Street  
Boston, MA 02109  
(617) 227-7400

**ADVANCED RESEARCH AND TECHNOLOGY INSTITUTE**

By:



Typed Name: Mark S. Long

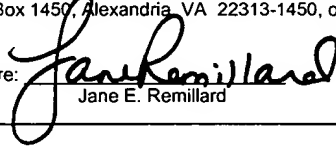
Title: President and CEO

Dated: 12/29/03

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EL982739183US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: January 9, 2004

Signature:

  
Jane E. Remillard

Docket No.: PPI-007  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of: Roger W. Roeske

U.S. Patent No: 5,843,901

Issued: December 1, 1998

For: LHRH ANTAGONIST PEPTIDES

MailStop Patent Ext.  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**POWER OF ATTORNEY**

Dear Sir:

Praecis Pharmaceuticals, Inc., the exclusive licensee and agent acting on behalf of the owner, Advanced Research and Technology Institute, of the above-identified patent, hereby appoints the below listed attorneys with full power to prosecute the above-referenced patent and to transact all business in the Patent Office connected therewith.

|                        |                 |                                |                           |
|------------------------|-----------------|--------------------------------|---------------------------|
| James E. Cockfield     | Reg. No. 19,162 | Maria C. Laccotripe Zacharakis | Limited Recognition       |
| Thomas V. Smurzynski   | Reg. No. 24,798 |                                | Under 37 C.F.R. § 10.9(b) |
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| Anthony A. Laurentano  | Reg. No. 38,220 | Theodore R. West               | Reg. No. 47,202           |
| Kevin J. Canning       | Reg. No. 35,470 | Hathaway P. Russell            | Reg. No. 46,488           |
| Jane E. Remillard      | Reg. No. 38,872 | John S. Curran                 | Reg. No. 50,445           |
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